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THE AMERICAN ASSOCIATION FOR THE ADVANCEMENT OF SCIENCE

REPORT OF THE EXECUTIVE COMMITTEE

AT the meeting of the Executive Committee (members present, Roger Adams, O. W. Caldwell, A. J. Carlson, *chairman,* B. E. Livingston, Kirtley F. Mather, Walter R. Miles, F. R. Moulton and E. C. Stakman) held on June 24, 1945, the following actions were taken:

1. The Association will take over the editorship of SCIENCE January 1, 1946.

2. The nominees for consideration in connection with the editorship of SCIENCE secured by the Special Committee (Drs. George A. Baitsell, Philip Bard, Howard P. Barss, W. F. G. Swann) from the canvass of the members of the Council and submitted to the Executive Committee, were subjected to a preferential ballot and the chairman of the Executive Committee was authorized to contact these nominees in the order of the preference ballot, with reference to availability, and to report to the Executive Committee.

3. The chairman and the Permanent Secretary were authorized to submit the names of nominees for editorial advisers for SCIENCE (two nominees from each section, one to be elected), which were presented to the Executive Committee by the SCIENCE Policy Committee (Malcolm H. Soule, Roger Adams, Walter R. Miles), to the members of the Council for election.

4. The chairman was authorized to appoint a committee to study and make proposals for the acquisition of adequate housing facilities for the growing activities of the Association, and this committee was authorized to proceed immediately to secure funds for a permanent home for the Association.

5. The Philosophy of Science Society (membership 237, of whom 101 are members and 73 are fellows of the Association) was accepted as an affiliated society.

6. In compliance with the ruling of the ODT, the Association plans for no general meetings prior to the summer of 1946. However, the committee authorized: (a) the Permanent Secretary to arrange for two conferences of secretaries of sections and of principal affiliated societies, one conference to be held in the East, and one in the Midwest in the coming autumn or winter; (b) a committee (F. R. Moulton, Howard A. Meyerhoff, O. W. Caldwell, W. E. Wrather and Sam Woodley) to cooperate with appropriate local scientific organizations in holding meetings in localities throughout the United States during the academic year 1945–46. This committee was instructed to arrange at such meetings, wherever possible, at least one session devoted to consideration of the problems of organization of science and scientists in the years immediately following the war.

7. The Chairman, the General Secretary, and the Permanent Secretary were authorized to appoint a managing committee and to secure funds for an Annual Science Writers Award.

8. A plan was approved for a survey of local amateur science societies under the direction of the Permanent Secretary.

F. R. MOULTON,
Permanent Secretary

MEETINGS DURING 1945–1946

ON June 24, the Executive Committee unanimously adopted a report by Kirtley F. Mather on meetings of the American Association for the Advancement of Science during 1945 and 1946. The text of the report is of interest to all scientists and is herewith printed in full. The three motions which conclude Dr. Mather's statement were passed without a dissenting vote.

(*Report by Kirtley F. Mather, June 24, 1945*)

There is no reason to expect any relaxation of the ODT restrictions on travel before the spring of 1946 at best. The Executive Committee might well decide now that no general sessions of the American Association for the Advancement of Science will be held either in September, 1945, or December–January, 1945–46, and announce this decision to the members of the Association. This will clear the way for the planning of several regional meetings during the period between September, 1945, and May, 1946.

Such regional meetings should be on a "catch as catch can" basis, organized in cooperation with appropriate and available local societies. Where possible, meetings should be arranged by a regional association such as a State Academy of Science that has a broad coverage of many scientific fields. [The American Academy of Arts and Sciences (an organization that for all practical purposes takes the place of a hypothetical Massachusetts–Rhode Island Academy of Science) is already prepared to assist in organizing a joint meeting in Boston.] In certain regions the local sponsorship might be a specialized society, the secretary of which could serve as the key man for making local arrangements and the special field of which might be emphasized, but not to the exclusion of other disciplines, at the meeting.

Plans should include the objective of having a retiring vice-president for some appropriate section deliver his customary address at some one meeting. It should be the aim to cover all the sections and retiring vice-presidents during the year. Presumably in most cases the retiring vice-president would deliver his address at the meeting held in or very near his own place of residence.

The address of the retiring president should be delivered at a meeting held in cooperation with an inclusive organization. Possibilities are: in Boston, cooperating with the American Academy; in New York, cooperating with the New York Academy of Science; in Washington, Philadelphia or Chicago, cooperating with the local academy.

In announcing each meeting, attention should be specifically drawn to the ODT regulations limiting attendance to not more than 50 persons from beyond the regular commuting area surrounding the place of meeting. Ordinarily, only persons scheduled to appear upon the program should be permitted to come to meetings from beyond the commuting area and the number of such persons should be kept well below 50.

The American Association should appropriate money to cover the expenses of such meetings, and the national officers should accept a large share of responsibility for planning and organizing the meetings. Allotments should be made in advance by the office of the Permanent Secretary.

The following motions are proposed:

Moved, that, in accordance with the rulings of the Office of Defense Transportation, the American Association for the Advancement of Science make no plans for general meetings prior to the summer of 1946.

Moved, that the AAAS cooperate with appropriate local scientific organizations in holding regional meetings at several localities throughout the United States during the academic year 1945–46. To facilitate the organization of such meetings, a committee on regional meetings, consisting of the Permanent Secretary (Dr. Moulton), the Executive Secretary (Dr. Meyerhoff), the General Secretary (Dr. Caldwell), the Executive Assistant (Mr. Woodley) and the Treasurer (Dr. Wrather), be and hereby is appointed. This committee is hereby authorized to allot and expend funds totalling in the aggregate not more than $2,500.00 toward the expenses of such meetings.

Moved, that wherever possible the regional meetings include at least one session to be devoted to the consideration of problems pertaining to the role and organization of science and scientists in the years immediately following the termination of the war.

SUMMARY OF THE REPORT TO THE PRESIDENT ON A PROGRAM FOR POSTWAR SCIENTIFIC RESEARCH BY VANNEVAR BUSH, DIRECTOR OF OSRD

SCIENTIFIC PROGRESS IS ESSENTIAL

PROGRESS in the war against disease depends upon a flow of new scientific knowledge. New products, new industries and more jobs require continuous additions to knowledge of the laws of nature, and the application of that knowledge to practical purposes. Similarly, our defense against aggression demands new knowledge so that we can develop new and improved weapons. This essential new knowledge can be obtained only through basic scientific research.

Science can be effective in the national welfare only as a member of a team, whether the conditions be peace or war. But without scientific progress no amount of achievement in other directions can insure our health, prosperity and security as a nation in the modern world.

For the War against Disease. We have taken great strides in the war against disease. The death rate for all diseases in the Army, including overseas forces, has been reduced from 14.1 per thousand in the last war to 0.6 per thousand in this war. In the last 40 years life expectancy has increased from 49 to 65 years, largely as a consequence of the reduction in the death rates of infants and children. But we are far from the goal. The annual deaths from one or two diseases far exceed the total number of American lives lost in battle during this war. A large fraction of these deaths in our civilian population cut short the useful lives of our citizens. Approximately 7,000,000 persons in the United States are mentally ill and their care costs the public over $175,000,000 a year. Clearly much illness remains for which adequate means of prevention and cure are not yet known.

The responsibility for basic research in medicine and the underlying sciences, so essential to progress in the war against disease, falls primarily upon the medical schools and universities. Yet we find that the traditional sources of support for medical research in the medical schools and universities, largely endowment income, foundation grants, and private donations, are diminishing and there is no immediate prospect of a change in this trend. Meanwhile, the cost of medical research has been rising. If we are to maintain the progress in medicine which has marked the last 25 years, the Government should extend financial support to basic medical research in the medical schools and in universities.

For Our National Security. The bitter and dangerous battle against the U-boat was a battle of scientific techniques—and our margin of success was dangerously small. The new eyes which radar has supplied can sometimes be blinded by new scientific developments. V-2 was countered only by capture of the launching sites.

We can not again rely on our allies to hold off the enemy while we struggle to catch up. There must be more—and more adequate—military research in peacetime. It is essential that the civilian scientists continue in peacetime some portion of those contributions to national security which they have made so effectively during the war. This can best be done through a civilian-controlled organization with close liaison with the Army and Navy, but with funds direct from Congress, and the clear power to initiate military research which will supplement and strengthen that carried on directly under the control of the Army and Navy.

And for the Public Welfare. One of our hopes is that after the war there will be full employment. To reach that goal the full creative and productive energies of the American people must be released. To create more jobs we must make new and better and cheaper products. We want plenty of new, vigorous enterprises. But new products and processes are not born full-grown. They are founded on new principles and new conceptions which in turn result from basic scientific research. Basic scientific research is scientific capital. Moreover, we can not any longer depend upon Europe as a major source of this scientific capital. Clearly, more and better scientific research is one essential to the achievement of our goal of full employment.

How do we increase this scientific capital? First, we must have plenty of men and women trained in science, for upon them depends both the creation of new knowledge and its application to practical purposes. Second, we must strengthen the centers of basic research, which are principally the colleges, universities and research institutes. These institutions provide the environment which is most conducive to the creation of new scientific knowledge and least under pressure for immediate, tangible results. With some notable exceptions, most research in industry and in Government involves application of existing scientific knowledge to practical problems. It is only the colleges, universities and a few research institutes that devote most of their research efforts to expanding the frontiers of knowledge.

Expenditures for scientific research by industry and Government increased from $140,000,000 in 1930 to

$309,000,000 in 1940. Those for the colleges and universities increased from $20,000,000 to $31,000,000, while those for the research institutes declined from $5,200,000 to $4,500,000 during the same period. If the colleges, universities and research institutes are to meet the rapidly increasing demands of industry and Government for new scientific knowledge, their basic research should be strengthened by use of public funds.

For science to serve as a powerful factor in our national welfare, applied research both in Government and in industry must be vigorous. To improve the quality of scientific research within the Government, steps should be taken to modify the procedures for recruiting, classifying and compensating scientific personnel in order to reduce the present handicap of governmental scientific bureaus in competing with industry and the universities for top-grade scientific talent. To provide coordination of the common scientific activities of these governmental agencies as to policies and budgets, a permanent Science Advisory Board should be created to advise the executive and legislative branches of Government on these matters.

The most important ways in which the Government can promote industrial research are to increase the flow of new scientific knowledge through support of basic research, and to aid in the development of scientific talent. In addition, the Government should provide suitable incentives to industry to conduct research, (*a*) by clarification of present uncertainties in the Internal Revenue Code in regard to the deductibility of research and development expenditures as current charges against net income, and (*b*) by strengthening the patent system so as to eliminate uncertainties which now bear heavily on small industries and so as to prevent abuses which reflect discredit upon a basically sound system. In addition, ways should be found to cause the benefits of basic research to reach industries which do not now utilize new scientific knowledge.

We Must Renew Our Scientific Talent

The responsibility for the creation of new scientific knowledge—and for most of its application—rests on that small body of men and women who understand the fundamental laws of nature and are skilled in the techniques of scientific research. We shall have rapid or slow advance on any scientific frontier depending on the number of highly qualified and trained scientists exploring it.

The deficit of science and technology students who, but for the war, would have received bachelor's degrees is about 150,000. It is estimated that the deficit of those obtaining advanced degrees in these fields will amount in 1955 to about 17,000—for it takes at least six years from college entry to achieve a doctor's degree or its equivalent in science or engineering. The real ceiling on our productivity of new scientific knowledge and its application in the war against disease, and the development of new products and new industries, is the number of trained scientists available.

The training of a scientist is a long and expensive process. Studies clearly show that there are talented individuals in every part of the population, but with few exceptions, those without the means of buying higher education go without it. If ability, and not the circumstance of family fortune, determines who shall receive higher education in science, then we shall be assured of constantly improving quality at every level of scientific activity. The Government should provide a reasonable number of undergraduate scholarships and graduate fellowships in order to develop scientific talent in American youth. The plans should be designed to attract into science only that proportion of youthful talent appropriate to the needs of science in relation to the other needs of the nation for high abilities.

Including Those in Uniform. The most immediate prospect of making up the deficit in scientific personnel is to develop the scientific talent in the generation now in uniform. Even if we should start now to train the current crop of high-school graduates none would complete graduate studies before 1951. The Armed Services should comb their records for men who, prior to or during the war, have given evidence of talent for science, and make prompt arrangements, consistent with current discharge plans, for ordering those who remain in uniform, as soon as militarily possible, to duty at institutions here and overseas where they can continue their scientific education. Moreover, the Services should see that those who study overseas have the benefit of the latest scientific information resulting from research during the war.

The Lid Must Be Lifted

While most of the war research has involved the application of existing scientific knowledge to the problems of war, rather than basic research, there has been accumulated a vast amount of information relating to the application of science to particular problems. Much of this can be used by industry. It is also needed for teaching in the colleges and universities here and in the Armed Forces Institutes overseas. Some of this information must remain secret, but most of it should be made public as soon as there is ground for belief that the enemy will not be able to turn it against us in this war. To select that portion which should be made public, to coordinate its release, and definitely to encourage its publication, a board composed of Army, Navy and civilian scientific members should be promptly established.

A PROGRAM FOR ACTION

The Government should accept new responsibilities for promoting the flow of new scientific knowledge and the development of scientific talent in our youth. These responsibilities are the proper concern of the Government, for they vitally affect our health, our jobs and our national security. It is in keeping also with basic United States policy that the Government should foster the opening of new frontiers and this is the modern way to do it. For many years the Government has wisely supported research in the agricultural colleges and the benefits have been great. The time has come when such support should be extended to other fields.

The effective discharge of these new responsibilities will require the full attention of some over-all agency devoted to that purpose. There is not now in the permanent Governmental structure receiving its funds from Congress an agency adapted to supplementing the support of basic research in the colleges, universities and research institutes, both in medicine and the natural sciences, adapted to supporting research on new weapons for both Services, or adapted to administering a program of science scholarships and fellowships.

Therefore I recommend that a new agency for these purposes be established. Such an agency should be composed of persons of broad interest and experience, having an understanding of the peculiarities of scientific research and scientific education. It should have stability of funds so that long-range programs may be undertaken. It should recognize that freedom of inquiry must be preserved and should leave internal control of policy, personnel and the method and scope of research to the institutions in which it is carried on. It should be fully responsible to the President and through him to the Congress for its program.

Early action on these recommendations is imperative if this nation is to meet the challenge of science in the crucial years ahead. On the wisdom with which we bring science to bear in the war against disease, in the creation of new industries and in the strengthening of our Armed Forces depends in large measure our future as a nation.

THE RENAL REGULATION OF ACID BASE BALANCE WITH SPECIAL REFERENCE TO THE MECHANISM FOR ACIDIFYING THE URINE. II

By Dr. ROBERT F. PITTS

ASSOCIATE PROFESSOR OF PHYSIOLOGY, CORNELL UNIVERSITY COLLEGE OF MEDICINE

(*Continued from page 54*)

While the negative a pects of these experiments are obvious, what positive facts are proven? As I mentioned before, there are only two sources of acid of significant magnitude in a protein-free filtrate of plasma, namely, monobasic phosphate and carbonic acid. Hence only these two acids appear in the glomerular filtrate in appreciable amounts. Their sum is only one fourth to one third of the observed excreted titratable acid. Therefore the renal tubules must have added no less than two thirds to three fourths of the excreted acid to the filtrate as it passed down the tubular lumen. There is reason from work of the school of Dr. Richards on the frog for believing that the tubules add all the acid which appears in the urine.

If the proximal and distal segments of the amphibian kidney and the mammalian kidney are homologous, as seems probable from comparative physiological studies, then acidification of the urine in the dog as in the frog should take place in the distal tubule. There are two types of cellular mechanisms, illustrated in the two diagrams in Fig. 3, which could bring about this process of acidification: first, a true secretory mechanism, illustrated on the left, by which acid in molecular form could be secreted into the tubular lumen; and second, a quasi-secretory tubular mechanism, illustrated on the right, which could bring about an exchange of hydrogen ions for sodium ions. At first glance these two mechanisms seem very dissimilar. However, our attempts to distinguish between them experimentally have convinced us that a distinction is largely academic, and with present methods, impossible of achievement. If molecular acid were secreted, that acid might be hydrochloric, as

POSSIBLE MECHANISMS FOR THE TUBULAR EXCRETION OF ACID

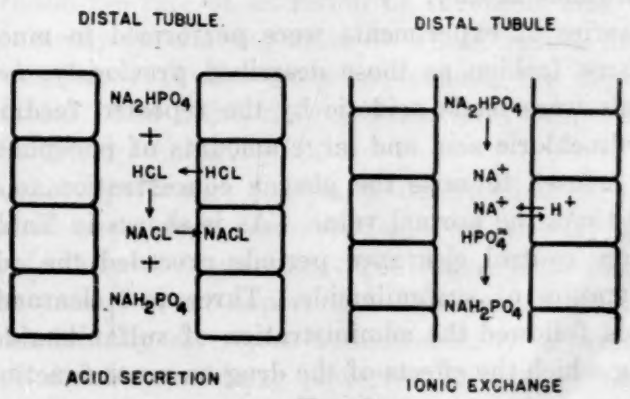

FIG. 3.

shown in this chart in the diagram on the left, or it might equally well be carbonic acid. Such acid could react within the tubule to transform dibasic sodium phosphate into the monobasic salt. In this process sodium chloride or sodium bicarbonate would be formed, and these salts might be expected to appear in the urine. In our experiments large quantities of titratable acid have been excreted, yet the urine has often contained neither chloride nor bicarbonate. Hence if any sodium chloride or any sodium bicarbonate were formed within the renal tubule, it must have been reabsorbed completely. Therefore it is apparent that even the acid secretory mechanism would to all intents and purposes accomplish an exchange of hydrogen ions for sodium ions. For certain indirect reasons which we need not consider here, we prefer the concept illustrated in the diagram on the right, namely, the direct exchange of hydrogen ions for sodium ions across the lumenal membrane.

The ultimate source of hydrogen ions which are added to the glomerular filtrate in its passage through the renal tubule must be carbonic acid. No other source of acid of sufficient magnitude is available to the kidney. Wherever it is necessary to hydrate carbon dioxide to form carbonic acid in large quantities, one finds the enzyme carbonic anhydrase. Thus the red cell,[9] the pancreas,[10] the stomach[11] and the kidney[12] all contain this enzyme in high concentration. It is possible that the carbonic anhydrase found in the kidney may in some way be involved in the cellular processes concerned with acidifying the urine. A mode of experimental attack was suggested by experiments of Mann and Keilin,[13] who found that sulfanilamide in low concentration added to preparations of carbonic anhydrase *in vitro* completely inhibited the enzyme. If the enzyme of the kidney is concerned in the renal excretion of acid, then the administration of sulfanilamide should reasonably be expected to raise the pH of the urine and to decrease its titratable acidity.

A series of experiments were performed in much the same fashion as those described previously, *i.e.*, animals were made acidotic by the repeated feeding of hydrochloric acid and large amounts of phosphate were infused to raise the plasma concentration to 9 or 10 times the normal value. As is shown in Table 7, three control clearance periods preceded the administration of sulfanilamide. Three test clearance periods followed the administration of sulfanilamide, during which the effects of the drug on renal function could be observed. The changes produced by sulfanilamide in urine pH, fourth column, and in titratable acid, fifth column, were striking. The pH of the urine rose from 5.6 to 6.8 after the administration of sulfanilamide, and the titratable acid decreased to about one third of the control value. These are exactly the changes which we predicted from the *in vitro* studies of Mann and Keilin, and are reminiscent of the effects of sulfanilamide on gastric secretion of acid first demonstrated by Davenport.[14]

TABLE 7

THE EFFECT OF SULFANILAMIDE ON THE RENAL EXCRETION OF TITRATABLE ACID BY THE ACIDOTIC DOG. IN THIS EXPERIMENT THE MAJOR URINARY BUFFER WAS PHOSPHATE

Rate of glomerular filtration cc/min.	Plasma concentration		Urine pH	Titratable acid		
	Phosphate	Sulfanilamide		Observed	Calculated	
	mM/L.	mg per cent.		mEq./min.	mEq./min.	Per cent. of observed
69.8	9.35	...	5.55	0.435	0.431	99.1
74.3	9.48	...	5.57	0.466	0.467	100.2
74.8	9.67	...	5.61	0.478	0.471	98.6
76.9	9.90	54.0	6.67	0.234	0.243	103.8
75.6	10.1	66.0	6.77	0.199	0.207	104.0
71.6	10.7	78.4	6.81	0.177	0.186	105.0

The effects of sulfanilamide are even more striking in an experiment shown in Table 8, in which creatinine rather than phosphate served as the major urinary buffer. Large amounts of creatinine were infused to raise the plasma concentration to approximately 130 mgm per cent. and hence to cause the excretion of large amounts of this buffer. Creatinine is less effective as a urinary buffer than is phosphate, thus the control values for titratable acid were lower. The effect of sulfanilamide was to raise urinary pH almost to the level of plasma pH and to decrease the

TABLE 8

THE EFFECT OF SULFANILAMIDE ON THE RENAL EXCRETION OF TITRATABLE ACID BY THE ACIDOTIC DOG. IN THIS EXPERIMENT THE MAJOR URINARY BUFFER WAS CREATININE

Rate of glomerular filtration cc/min.	Plasma concentration		Urine pH	Titratable acid		
	Creatinine	Sulfanilamide		Observed	Calculated	
	mg per cent.	mg per cent.		mEq./min.	mEq./min.	Per cent. of observed
96.7	131	...	5.76	0.148	0.154	104.0
96.6	128	...	5.76	0.150	0.152	101.4
89.4	126	20.2	5.95	0.094	0.091	96.8
100.0	129	27.4	6.29	0.050	0.049	102.0
93.8	135	36.4	6.69	0.019	0.021	110.0
90.6	138	43.7	7.16	0.003	0.003	100.0

[9] N. U. Meldrum and F. J. W. Roughton, *Jour. Physiol.*, 80: 113, 1933.

[10] H. vanGoor, *Arch. internat. physiol.*, 45: 491, 1937.

[11] H. W. Davenport, *Jour. Physiol.*, 97: 32, 1940.

[12] H. W. Davenport and A. E. Wilhelmi, *Proc. Soc. Exp. Biol. and Med.*, 48: 53, 1941.

[13] T. Mann and D. Keilin, *Nature*, 146: 164, 1940.

[14] H. W. Davenport, *Amer. Jour. Physiol.*, 133: 257, 1941.

observed titratable acidity of the urine almost to zero. These experiments are certainly consonant with the view that carbonic anhydrase is involved in some way in the mechanism for acidifying the urine.

Our concepts of the nature of this cellular mechanism are outlined in schematic form in Fig. 4. We have illustrated here a single cell from that part of the distal segment of the renal tubule which is concerned with acidification of the urine. On the left is the lumenal border of the cell in contact with the tubular urine. On the right is that border of the cell which is in diffusion equilibrium with the renal tubular blood. Carbon dioxide is produced within the tubular cell by oxidative metabolic processes and may also diffuse into the cell from the peritubular blood. This carbon dioxide is hydrated to form carbonic acid. The enzyme carbonic anhydrase serves to increase catalytically the rate of production of car-

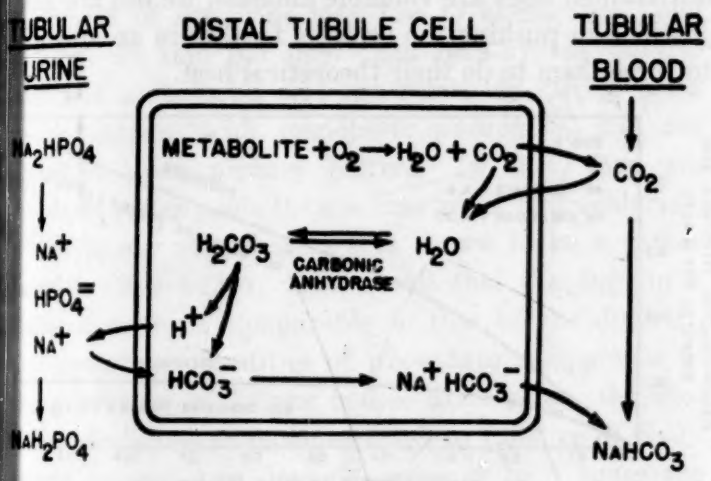

FIG. 4. Diagrammatic representation of the nature of the renal cellular mechanism for acidifying the urine. A single cell from the distal segment of the renal tubule is illustrated. From Pitts, R. F. and Alexander, R. S., *Amer. Jour. Physiol.*, 144: 239, 1945.

bonic acid, but is of course not essential for the process of hydration. Thus when carbonic anhydrase is inhibited by sulfanilamide,[15] hydration of carbon dioxide and excretion of acid continue, although at a slower rate. Carbonic acid dissociates within the cell to form hydrogen ions and bicarbonate ions; the hydrogen ions are exchanged for sodium ions in the tubular lumen; and the sodium ions, accompanied by an equivalent number of bicarbonate ions, are reabsorbed into the tubular blood. While the details of this scheme are largely hypothetical, it has the virtue of explaining adequately the known facts concerning the excretion of titratable acid, namely, that hydrogen ions are added to the tubular urine by the renal tubular cells, that an equivalent amount of base is retained in the body, and that the enzyme carbonic anhydrase is in some way concerned in the process.

Acidification of the urine is a process which requires the expenditure of energy, *i.e.*, the exchange of ions will not proceed spontaneously. Thermodynamically, the energy expended to cause this movement of ions must at least equal the heat of neutralization of the acid which is excreted. Since biological processes are never 100 per cent. efficient, the actual cellular work done will be several times this value.

The failure of this acid-excreting mechanism in nephritis is obviously one cause of the acidosis which characterizes the terminal stages of this disease. In chronic diffuse glomerulonephritis the number of functional nephrons is of course markedly reduced. Ordinarily one considers that the reduced excretory capacity of the kidney and the consequent retention of phosphate and sulfate in the blood stream adequately account for the acidosis. I wonder, however, if in addition to the obvious morphological lesion in this disease, there may not also be a biochemical lesion of the renal tubular cells. By this I mean that the disease process might adversely affect the functional capacity of the tubular cells of the remaining nephrons. It might do so by reducing their ability to do the work involved in acidifying the urine, or by reducing the efficiency with which they perform ionic exchanges. Furthermore it is possible that the disease process might bring about a reduction in the intracellular concentration of carbonic anhydrase, and thus specifically reduce the capacity of the tubular cells to produce hydrogen ions at a rapid rate.

In the remaining time at my disposal I should like to discuss briefly the factors which determine the rate of excretion of titratable acid and the bearing which these factors have on the renal response to acidosis in diabetes. There are three major factors which determine the rate of excretion of titratable acid by the normally functioning kidney. These include first, the quantity of buffer excreted; second, the degree of acidosis; and third, the physiochemical properties of the urinary buffer.

In the experiments now to be described as in the previous ones, dogs were rendered acidotic by the daily feeding of dilute acid. The degree of acidosis of the animal in the experiment illustrated in Fig. 5 was moderately severe, as is indicated by a plasma carbon dioxide combining power of 22 vol. per cent. The normal for the dog as for the human is between 50 and 60 vol. per cent. A series of solutions of neutral sodium phosphate of increasing concentration were infused intravenously, causing the animal to excrete progressively increasing amounts of buffer over a range of one tenth to eight tenths of a millimol

[15] According to a recent study of Davenport (*Jour. Biol. Chem.*, 158: 567, 1945), the sulfanilamide concentrations attained in our experiments (20 to 78 mg per cent.) should inhibit 99.93 to 99.97 per cent. of the carbonic anhydrase present in the kidney. However, the minute fraction of the enzyme which remains active (0.03 to 0.07 per cent.) probably accounts for the residual acid excretion which we have observed.

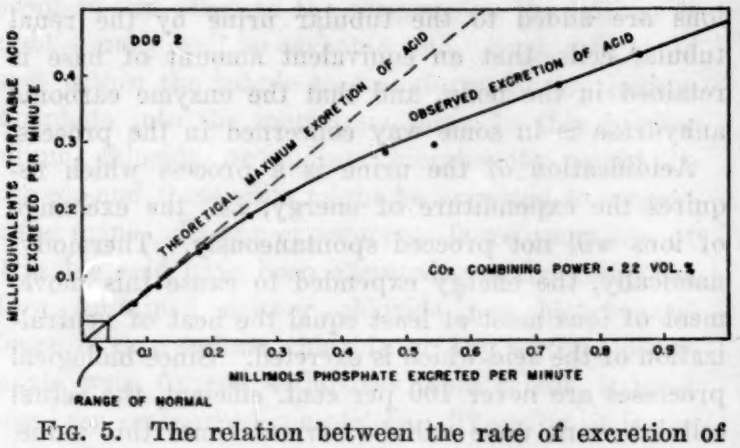

FIG. 5. The relation between the rate of excretion of titratable acid and the rate of excretion of phosphate in the acidotic dog.

of phosphate per minute. In this and in the succeeding two figures we have plotted the milliequivalents of titratable acid excreted per minute against the millimols of buffer excreted per minute. It is apparent that the rate of excretion of titratable acid progressively increased with the increase in the rate of excretion of phosphate. The dashed line labelled the *theoretical maximum excretion of acid* is that amount which would have been eliminated if in each instance the animal had produced urine of maximal acidity, *i.e.*, urine of pH 4.8. Actually you see that the greater the excretion of phosphate the greater is the deviation from the theoretical maximum rate of excretion of acid. In other words, the more phosphate that is presented to the kidney, the less completely does the kidney utilize its full buffer potentialities. The maximum observed rate of acid excretion in the experiment shown in Fig. 5, namely, 0.431 milliequivalents per minute, is equivalent to the excretion of 6,200 cc of N/10 acid per day. In the lower left-hand corner of the chart is a small rectangle which indicates the range of excretion of phosphate and titratable acid in normal man. It is apparent that the quantity of titratable acid which the kidney can excrete under stress is far greater than the quantity which is normally excreted, and that a major factor which limits acid excretion is the quantity of buffer available in the urine.

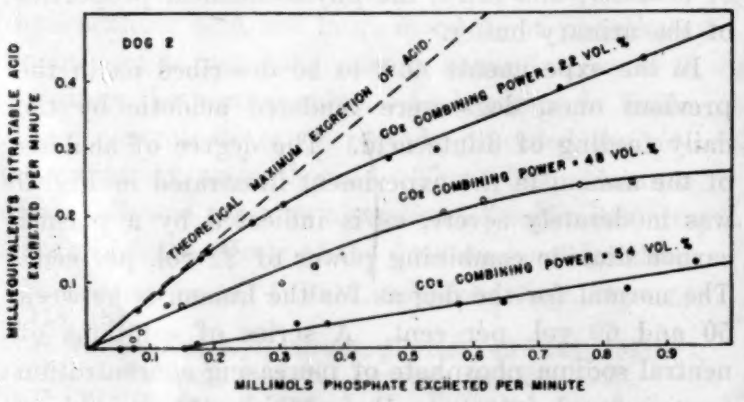

FIG. 6. The relation between the rate of excretion of titratable acid and the serverity of the acidosis in the acidotic dog.

The second factor determining the rate of excretion of titratable acid is the degree of acidosis. Three experiments similar to the one just presented were performed on a single dog. The results obtained in these experiments are summarized in Fig. 6. In the different experiments the degree of acidosis was varied by altering the total amount of acid fed to the animal. The carbon dioxide combining power noted on each experimental curve indicates the severity of the acidosis. A combining power of 54 vol. per cent. is within the range of normal for the dog. A combining power of 22 vol. per cent. is indicative of a moderately severe acidosis. It is apparent at any given rate of excretion of phosphate that the more severe the acidosis, the greater is the excretion of titratable acid. It is interesting to note that the more severe the acidosis, the more nearly the kidney approaches the theoretical maximum rate of excretion of acid. Since our trained dogs are valuable animals, we did not feel justified in pushing the acidosis further in an attempt to force them to do their theoretical best.

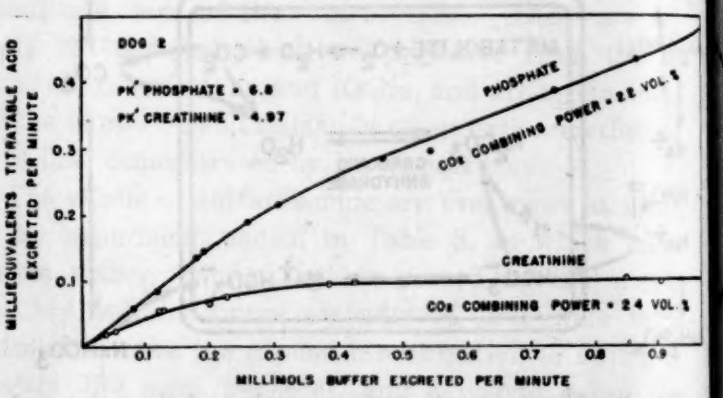

FIG. 7. The relation between the rate of excretion of titratable acid and the strength of the buffer acid excreted in the acidotic dog.

The third factor determining the rate of excretion of titratable acid is the strength of the buffer acid excreted. A convenient designation of the strength of a weak acid is its pK′ value. The pK′ of an acid is the pH which is observed when the acid is exactly half neutralized. Therefore the lower the pK′, the stronger is the acid. The physiologically important hydrogen of phosphate is the second one, and its pK′ is 6.8; *i.e.*, when half of the monobasic phosphate in a solution is neutralized to the dibasic form, the pH of the mixture is 6.8. The pK′ of creatinine is 4.97; *i.e.*, when half of the creatinine is in the form of free base and half is in the acid form, say of creatinine hydrochloride, the pH of the mixture is 4.97. Accordingly monobasic phosphate is a much weaker acid than is creatinine hydrochloride. From Fig. 7 it is apparent that phosphate is a far better urinary buffer than is creatinine, and that when equi-molar quantities of these two buffers are presented to the kidney, the excretion of acid is far greater with phosphate than with creatinine.

The bearing of these results on the renal excretion of acid in diabetic acidosis is rather direct. Thus the uncontrolled diabetic excretes large quantities of buffer in the form of beta-hydroxybutyrate and acetoacetate; as much as 500 to 1,000 millimols of these buffer substances may be excreted in 24 hours. You recall that the rate of excretion of titratable acid in our experiments was directly related to the rate of excretion of buffer. Likewise the severity of the acidosis is often very great in the uncontrolled diabetic and plasma carbon dioxide combining powers as low as 10 to 20 vol. per cent. are not uncommon. Again you recall that the rate of excretion of titratable acid in our acidotic dogs was directly related to the severity of the acidosis. Both factors, the high rate of buffer excretion and the severity of the acidosis, combine to stimulate the renal excretion of titratable acid in the diabetic. Accordingly the titratable acid of the urine may rise to as high as 1,500 cc of N/10 acid per day. But beta-hydroxybutyric acid and acetoacetic acid are relatively strong acids in comparison with monobasic phosphate, and are therefore poor urinary buffers. In fact, they are stronger buffer acids than is creatinine hydrochloride, which in our experiments was shown to be a rather poor urinary buffer. You recall that the dog, in a state of acidosis comparable to that of the diabetic, and excreting quantities of phosphate comparable to the quantities of ketone bodies excreted by the diabetic, eliminates as much as 6,000 to 7,500 cc of N/10 titratable acid per day, *i.e.*, some 4 to 5 times the quantity eliminated by the diabetic. This quantitative difference is certainly related to the strength of the buffer acid excreted and not to a greater effectiveness of the acid-eliminating mechanism in the dog. Since the capacity of the renal tubules to excrete relatively strong acids such as beta-hydroxybutyric and acetoacetic in free titratable form is limited, the kidney must excrete them in large part combined with fixed base. Accordingly the alkali reserve of the body is progressively exhausted, and terminally the acidosis of diabetes may become extreme.

In conclusion let me summarize briefly our concepts of the renal mechanism for excretion of titratable acid, and the nature of the aberrations of this mechanism in disease. A slightly alkaline filtrate of plasma containing buffer acids in combination with sodium ions is formed in the glomeruli. In the passage of this alkaline filtrate through the distal segments of the renal tubules hydrogen ions formed within the tubular cells are exchanged for sodium ions in the tubular urine. The urine becomes acid by the conversion of buffer salts to free buffer acids, and base is saved by the reabsorption into the renal venous blood of sodium ions along with equivalent numbers of bicarbonate ions.

The quantity of base which is saved, or conversely the quantity of free titratable acid which is excreted by this mechanism, is determined by three major factors: first, the quantity of buffer available for the kidney to operate upon; second, the strength of the buffer, *i.e.*, how strongly it resists giving up its sodium ions in exchange for hydrogen ions; and third, the severity of the acidosis, which is of course a measure of the need of the body for the conservation of its basic constituents.

Under normal conditions the capacity of the kidney to exchange hydrogen ions for sodium ions is sufficient to permit the excretion of the fixed metabolic acids without depletion of the body stores of fixed base. But in diabetes the excessive production of metabolic acid so overwhelms the renal mechanism that it is incapable of full compensation, and progressive acidosis develops. One reason for the failure of compensation is the rather unfavorable physiochemical properties of two of the buffer acids formed in this disease, beta-hydroxybutyric and acetoacetic acids. Both acids are too strong for the kidney to operate on effectively.

In nephritis the mass of functional renal tissue is reduced. Therefore each remaining unit must carry more than its normal share of the burden of acid elimination. Furthermore, it is probable that the disease process has reduced the capacity of these remaining units to excrete acid as compared with the capacity of normal units. Perhaps it has done so by restricting the chemical work which the renal tubular cells can do, or perhaps the disease process has specifically reduced the cellular content of the vital enzyme carbonic anhydrase.

I am sure that much of what I have said concerning the overall aspects of the renal regulation of acid base balance is familiar to you all. However, I have tried to emphasize the dynamic aspects of the problem, for acid-base regulation is most certainly concerned with the moment to moment maintenance of balance. If I have given you a more fluid concept of the problem, I have accomplished my major aim. My secondary aim has been to show you how recently developed methods of study of the kidney may be applied to the solution of basic problems of renal physiology, and how they in turn may throw light on certain abnormalities of function in disease. But I admit frankly that more questions have been raised concerning renal physiology in nephritic and diabetic acidosis than have been answered. It is our hope, by continuing our studies on patients with these two diseases, that we shall be able to provide a direct answer to some of the more puzzling of these clinical physiological questions.

OBITUARY

CURTIS J. HESSE

WITH the death of Curtis J. Hesse, curator of the Museum of the Agricultural and Mechanical College of Texas, not only has the museum lost an excellent custodian and the college an able geologist, but the community has lost a congenial friend.

Mr. Hesse was born on September 28, 1905, in Wamego, Kansas, and died at Bryan, Texas, on May 12, 1945, after recurring heart attacks. He is survived by his mother, Mrs. C. V. Hesse, and a brother, C. G. Hesse, both of Lawrence, Kansas.

Mr. Hesse entered the field of paleontology when he was 14 years of age, at which time he became connected with the Museum of Paleontology at the University of Kansas, and held this position until 1929. During the time he was with the University of Kansas Museum, Mr. Hesse completed work for his bachelor of arts degree, which was conferred by the university in 1927. In 1929, he went to the University of California on a teaching fellowship and later became laboratory and field assistant for the Museum of Paleontology. During his connection with the University of California, he received his master of arts degree in 1933.

In 1938, Mr. Hesse came to Texas A. and M. as assistant curator of the museum and in 1943 he was made curator, which position he held until the time of his death. In addition to duties with the operation of the museum and field trips over Texas and other states in its interest, Mr. Hesse gave a portion of his time to work on the teaching staff of the department of geology. Even though he carried a full schedule with his teaching load and work at the museum, still he found time for numerous articles on the results of research which he was conducting in different phases of geology. The esteem in which he was held by his colleagues and students and the papers he has contributed to important scientific journals are a tribute to his scientific accomplishment and inspirational force.

Mr. Hesse was secretary of the Texas A. and M. Chapter of the American Association of University Professors, treasurer of the Texas Academy of Science, and held membership in the American Association of Petroleum Geologists, American Association for the Advancement of Science, Geological Society of America, American Society of Vertebrate Paleontologists, Texas Archeological and Paleontological Society, Sigma Xi, Texas Geographic Society, American Society of Mammalogists and the American Society of Economic Paleontologists and Mineralogists.

His services to these organizations are evidence of his willingness to contribute beyond the line of duty to the advancement of scientific endeavor.

To his scholarship was added an intense interest in the development of good citizenship in American youth. He gave much of his time to fostering Boy Scout activities in this section of the state and in this capacity became a leader. He was Scoutmaster for Troop 102 of College Station, which maintained headquarters in the museum. Mr. Hesse had the reputation of being one of the best and most efficient scoutmasters in this area and his troop was regarded as a model for proper scouting activities.

Being always ready to address the boys and girls of Bryan and College Station schools, he was frequently called upon and prepared for these talks in the spirit of embracing an opportunity to turn the thoughts of youth in the right direction.

Mr. Hesse possessed the admirable characteristics of being trustworthy, helpful, friendly, courteous, kind and cheerful. With these traits, it is not extraordinary that his personality won him the friendship of his associates.

HAROLD VANCE

AGRICULTURAL AND MECHANICAL
COLLEGE OF TEXAS

SCIENTIFIC EVENTS

GERMAN UNIVERSITIES AND MUSEUMS

DR. JOHN W. WELLS, of the department of geology of the Ohio State University, has sent to SCIENCE the following information in regard to German universities and museums:

Jena: Mineralogisches Institut totally demolished and apparently not wholly evacuated before the main bombing three weeks before the capture of the city. Geographisches Anstalt somewhat damaged by blast, mostly evacuated. The building temporarily houses the Geologisches Institut of the University of Breslau.

Erlangen: Undamaged. Nothing evacuated from Geologisches Institut. Most of staff, with exception of Krumbeck and another, in German army.

Heidelberg: Undamaged, but most of collections of the Geologisches-Paläontologisches Institut evacuated, including large quantities of material from the Mauer deposits. For last few years there have been three regular staff members, of whom only one, Florian Heller, was there at time of visits. The head of the Institut is Wilser; additional teaching aid was given by Salomon and Jaworski.

Wurzburg: Geographisches Institut completely demolished, but most of equipment apparently moved to the country. Geologisches Institut slightly damaged by blast, nothing evacuated, and, being one of the few habitable buildings in the city, was being used for army billets.

Darmstadt: Geologisches Institut and Hessisches Geologisches Landesanstalt totally demolished.

Frankfurt a/M.: Geologisches Institut of Goethe Universität wholly demolished. Senckenberg Museum in very bad shape, reduced almost to a hollow shell, but research collections, stocks of publications and library are safe. R. Richter, the director, was in Bucharest at time of capitulation of that city, and is now interned by the Russians. In 1943 he published a long paper on the rules of nomenclature and nomenclatural problems. The director *pro tem* is Reuling. The only actual losses at the Senckenberg, aside from the building itself, were a large number of large plaster casts, including the large one of *Diplodocus carnegiei*, the type specimen of *Hallotherium*, and a large ornithological collection.

Bonn: Geographisches Institut a total loss, but material mostly evacuated across the Rhine. Geologisches-Paläontologisches Institut slightly damaged by blast, but all important collections, including that of Goldfuss, safely evacuated. Cloos is still director.

Cologne: Geographisches Institut in bad shape, not evacuated.

Munich: The main university building is very badly damaged. Geographisches Institut relatively undamaged, but rooms have been taken over by the Universitäts Kanzlei. Technische Hochschule not badly damaged; Wilhelm Credner, of the Geographisches Institut, has been very active during the war, like most German geographers. The Bayerische Akademie building is a total wreck, and of the vast geological, paleontological and mineralogical collections, only about 250 cases, a very small part, were saved. All the fossil vertebrate collections were destroyed, as was also the Zittel Collection. The building of the Geographisches Gesellschaft was wholly destroyed and the entire library lost. At the Bavarian Geological Survey, two geologists, one Dutch, one German, reported that they had been in Berlin as late as February, 1945. The Preussische Geologische Landesanstalt and the Museum für Naturkunde are quite destroyed. The library and archives of the former were safely evacuated, but only a few types were saved from the museum. The splendid skeleton of *Brachiosaurus* is lost. At that time both Schindewolf and Stille were well and active.

Innsbruck: University undamaged. Geographisches Institut, headed by Kinzi, in working condition, although most of non-current library was evacuated. From the Geologisches-Paläontologisches Institut in the Alte Universität, the collections and library were largely evacuated, and are now being moved back in. The Mineralogisches-Petrologisches, still presided over by Sander, is carrying on.

THE CHINESE JOURNAL OF PHYSICS

READERS of SCIENCE will be interested in the editor's note published in the *Chinese Journal of Physics*, Volume V, No. 1, July, 1944. This note gives us a slight indication of the difficulties under which scientists in China have been laboring. It reads as follows:

To the reading public of this journal, we owe a note of explanation. Since our last appearance there has been an extraordinarily long silence of nearly four years. Nevertheless, this is not to be interpreted as a suspension of publication by choice, nor any lack of enthusiasm in research work on the part of Chinese physicists, but rather a concrete example of the severity of wartime conditions. We have indeed tried to publish the No. 2 of Vol. 4 of this journal, to follow up the last issue (No. 1 of Vol. 4), at a time strangely coincident with the outbreak of the war in the Pacific (*i.e.*, December of 1941). Not only was the publication held up, but also the manuscripts and all other previous documents, including our only copies of the last issue of this journal, were utterly lost. Thus this child of ours was never born.

As time goes on, we find it more and more imperative to revive our publication as a channel of expressing our scientific endeavors, which have been maintained quite vigorously though in face of very great difficulties. The journal thus comes to life again as a response to this universal sentiment among the Chinese physicists. This time, however, we start with Vol. 5 anew, instead of finishing up the remaining numbers of Vol. 4, because we are unfortunately not in a position to designate the correct sequence for the new pages, not knowing what the page number of the last issue was. Incidentally, just to remind our readers and librarians, please note that there have been only two numbers (Nos. 1 and 2) to Vol. 3, due to some rather trivial reasons.

If apologies are in place, we wish to offer our humble ones for the poor printing, crude paper, typographical errors, irregular time of publication and countless other shortcomings. Much as we should like, we find ourselves quite powerless to combat these various troubles in times like these. May we also plead, for the sake of doing justice to our contributing authors, that the public will kindly grant the time of reception to be nearly the time of publication for, due to inadvertent delays, we feel that we are the guilty party. While the statement should apply in general, this present issue represents an almost absurd extreme, where the papers are just those of which the manuscripts were read for publication but finally lost three years ago.

J. W. BUCHTA

GRANTS OF THE SUGAR RESEARCH FOUNDATION

ADDITIONAL grants amounting to more than $50,000 for seven leading universities and laboratories have been made by the Sugar Research Foundation, bringing to the sum of more than $300,000 the grants made by the foundation.

Recipients of these grants include the Medical School of McGill University, the University of Pittsburgh, Yale University Medical School, the University of Utah, the New York University Medical School, the Cornell University Medical School and the Brooklyn Polytechnic Institute.

The studies will seek new industrial uses of sugar and further explore the nutritional values of sugar. Eight of the projects call for allotments of $41,500, and involve research into entirely new fields. An ad-

ditional $9,500 was recommended to continue experiments on projects already begun.

These studies, Dr. Robert G. Hockett, scientific director of the foundation, announced, implement the original program of scientific research and are designed to develop a further understanding, not only of the product itself, but of its effect on the human system. All possible fields of research have not yet been explored. Among other projects which the foundation might support, are studies for increasing the utilization of sugar for such diversified purposes as meat curing, tanning leather, fruit freezing and in insecticides, ice cream, baking, cattle feeding, metallurgy, electro-plating, paper sizing and producing silage from hay and grass.

Dr. Hockett announced grants to the following:

Dr. Hans Selye, associate professor of histology at the Medical School of McGill University, $10,000, for a three-year study of the effects of diets in protecting animals from the effects of over-activity of the endocrine glands.

Dr. I. M. Rabinowitch, associate professor of medicine at McGill University and director of the department of metabolism at the Montreal General Hospital, $10,000, for investigation of the use of sugars in human nutrition in health and in disease. Dr. Rabinowitch is in charge of the clinic for diabetes, which is the largest clinic of its kind in Canada.

Dr. Gebhard Stegeman, professor of physical chemistry at the University of Pittsburgh, $7,000, to collate all existing data and carry out new measurements of the physical properties of sugar and sugar solutions for use by industrial chemists.

Drs. F. W. Zerban and Louis Sattler, of the New York Sugar Trade Laboratory, $4,000, for further investigation of the unfermentable constituents of molasses. These investigators have made important contributions to the study of molasses, including identification of allulose as one of its constituents.

Dr. George R. Cowgill, professor of nutrition at Yale University Medical School, $3,600, to survey the vitamin content of various products of the sugar industry at the point when they reach the market. The survey will cover raw sugars, soft sugars, molasses, syrups, white sugars and high-test molasses.

Professor L. T. Samuels, head of the department of biochemistry at the University of Utah, $3,500, to study the capacity of animals to adjust themselves physiologically to various types of diets.

Dr. H. M. Wuest, of the Brooklyn Polytechnic Institute, $1,900, to study preparation of several compounds closely related to vitamin B_1 and study their effects on assay methods.

Drs. Walter D. Bonner and Ralph F. Phillips, of the department of chemistry of the University of Utah, $1,500, to study production of certain glucose derivatives directly from sugar and molasses.

In addition to the new grants, an additional $5,000 was awarded to Professor L. Emmett Holt, Jr., of the Medical School of New York University, to continue his work on the synthesis of vitamins in the intestinal tract under the influence of various diets.

A renewal of a $4,500 grant was given to Professor James M. Neill, of the department of bacteriology and immunology at the Cornell University Medical School.

GRANTS FROM THE PENROSE FUND OF THE AMERICAN PHILOSOPHICAL SOCIETY

AT a meeting on June 1 of the research committee of the American Philosophical Society the following grants were made from the Penrose Fund:

Kenneth W. Hunt, Preparation and completion of key and catalogue for the woody plants of Charleston County, $450.

Charles W. Metz, Analysis of evolutionary changes occurring within the chromosomes in Sciara, $1,000.

A. F. Blakeslee, Embryology in plants, especially in the genus Datura, $1,500.

Sister M. Inez Hilger, Ethnological field study of the beliefs, customs, etc., in the rearing and training of the Araucanian Indian child of Chile, $1,500.

Wallace Craig, The space system of the perceiving self, $1,250.

Philip P. Wiener, Intellectual developments in America surrounding Chauncey Wright and other members of the Metaphysical Club with respect to basic idea of evolutionism in the years 1850–1875, $1,000.

William J. Roach, Edition and critical study of the First Old French Continuation of the *Perceval* of Chretien de Troyes, $1,500.

Joseph E. Hellmer, Field study of regional Mexican folk music, $570.

Victor Zuckerkandl, To determine theoretically the function of music in the spiritual life of modern man, $600.

George Steindorff, Completion of Coptic Grammar in English, $600.

Lyman H. Butterfield, Survey of materials by and relating to Dr. Benjamin Rush, $200.

THE AMERICAN SOCIETY OF TROPICAL MEDICINE

AT the annual meeting held in St. Louis in November of the American Society of Tropical Medicine, of which Dr. R. E. Dyer is president, the report of the committee on war and postwar problems was presented and approved.

In this report, printed in *Tropical Medicine News*, the committee requested the Surgeon General of the U. S. Public Health Service:

(1) To organize teaching teams to visit laboratories in the states for the instruction of personnel in the techniques of laboratory diagnosis of tropical diseases.

(2) To disseminate appropriate articles on the diag-

nosis and treatment of tropical diseases to the practising physician.

(3) To form a library of teaching films to be loaned to medical societies and other appropriate organizations.

The Surgeon General agreed to sponsor the program and called upon Medical Director L. L. Williams, Jr., to formulate plans. The program, as originally proposed by Dr. Williams, provided for the recruiting and training of ex-servicemen as technicians to be assigned to state health department laboratories, these technicians to serve the States both in the laboratory diagnosis of tropical diseases and in training other technicians within the States. Dr. Williams's plan provided for lectures by teams of lecturers well qualified to cover the field of tropical medicine, who were to visit state and local medical societies.

Since the assignment of Dr. Williams to the Department of State, the carrying out of the program has been transferred to the Office of Malaria Control in War Areas (of the States Relations Division) in Atlanta, with Surgeon (R) William S. Boyd in charge.

The situation was canvassed in regard to the recruiting of personnel, particularly ex-servicemen, with the view of preparing these men for duty in state health department laboratories. It was soon realized that for the present it would not be possible to enlist a sufficient number of qualified men to carry on the program as originally planned. Therefore the decision was reached to set up in Atlanta expanded laboratory facilities to serve a threefold purpose:

(1) To offer intensive training in the laboratory diagnosis of tropical diseases.

(2) To serve as a diagnostic center for examination of specimens referred by state departments of health and for examinations of diagnostic materials obtained for survey purposes.

(3) To make available to technicians in state and local health department laboratories diagnostic and reference materials.

The first class for state laboratory technicians will be opened on October 1.

SCIENTIFIC NOTES AND NEWS

THE Baltimore Chapter of the American Institute of Chemistry recently presented to Dr. E. Emmet Reid, professor of chemistry emeritus of the Johns Hopkins University, an honorary membership scroll "in recognition of services as a scientist, industrialist, inventor, teacher and humanitarian."

THE fourth annual John Wesley Hyatt Award for outstanding achievement in the plastics industry was presented in New York on June 13 to William Iler Beach, chief plastics engineer of North American Aviation, Inc., Inglewood, Calif. Mr. Beach received the award for his work on the post forming of laminates, which made possible the manufacture of certain critically needed parts for the aircraft industry. The presentation of the gold medal and the sum of $1,000 was made by George K. Scribner, representing the John Wesley Hyatt Award Committee at a dinner given at the Waldorf-Astoria.

THE degree of doctor of science of Bucknell University was conferred on Dr. Doncaster G. Humm on June 23 in recognition of his work on "the standardization and validation of the Humm-Wadsworth Temperament Scale and its application to over three million industrial workers."

AT its sixty-eighth annual commencement on June 17, the University of Oregon conferred the doctorate of science on William Fitch Allen, professor of anatomy and head of the department at the Medical School, with the following citation: "In recognition of his notable contributions to the sciences of anatomy and physiology; the urge to research and productive scholarship implanted in the minds of generations of students; and his long and devoted career as teacher and mentor of medical men of the Pacific Northwest." The degree of doctor of laws was conferred on Lewis Ankeny McArthur, president of the Oregon Historical Society and author of "Oregon Geographical Names." The citation reads: "In recognition of his painstaking and fruitful researches into the origin of place names in Oregon; the lasting stimulus he gave to wide-spread popular interest in local history; and his continuing zeal for the social welfare manifested in manifold acts of public service."

LAVAL UNIVERSITY at its commencement exercises conferred the doctorate of science, *honoris causa*, on A. F. G. Cadenhead, director of the department of plant research at Shawinigan Chemicals, Ltd.

DR. J. E. W. WALLIN reached the retirement age in the Wilmington, Delaware, school system at the close of the scholastic year in June, but continues under the recently enacted State Retirement Act to serve the State Board of Education on a part-time basis as director of special education and mental hygiene. At a testimonial dinner on March 21, sponsored by Wilmington special education teachers, he was presented with a leather-bound volume containing 117 letters of appreciation from university presidents, deans and professors, public school superintendents, principals and teachers, clinic and research directors, and others from twenty-four states, Hawaii and the District of

Columbia. He was also presented with a framed illuminated scroll painted by Dr. Martin Jennings, of New York University.

THE following officers of the Illinois Institute of Technology Chapter of Sigma Xi have been elected to serve for the academic year 1945–46: *President,* Dr. Lester R. Ford, chairman of the department of mathematics; *Vice-president,* Dr. T. J. Higgins, associate professor of electrical engineering; *Secretary,* Dr. John De Cicco, assistant professor of mathematics, and *Treasurer,* Dr. L. R. Hedrick, professor of biology.

AT a recent meeting of the Chicago Section of the Electrochemical Society, the following officers were elected for the coming year: C. A. Getz, *Chairman;* C. W. Carter, *Vice-chairman;* J. Bjorksten, *Secretary,* and B. F. Freeberg, *Treasurer.*

PROFESSOR HENRY S. W. KEITH, head of the department of naval architecture and marine engineering of the Massachusetts Institute of Technology, will retire on January 1 with the title of professor emeritus after having been associated with the institute for thirty-nine years.

DR. EDWARD C. SCHNEIDER, Ayres professor of biology at Wesleyan University, has retired after serving for twenty-five years.

RETIREMENTS from the faculty of the University of Rochester include Dr. Arthur S. Gale, professor of mathematics, formerly dean; Dr. Edwin Fauver, director of physical education and college physician; Floyd C. Fairbanks, professor of physics and astronomy, and, as already announced, Dr. John R. Murlin, professor of physiology.

DR. HAROLD HOWE, professor of agricultural economics at Kansas State College, has been appointed dean of the graduate school. Dr. Howe succeeds Dr. James E. Ackert, who has been dean since 1931 and who, in accordance with the state's policy of relieving officers of their administrative duties at the age of sixty-five years, has also resigned as head of the department of zoology. Dr. Donald J. Ameel has been promoted to a full professorship in the department of zoology and has been appointed acting head of the department.

DR. CLARENCE DORMAN, director of the Agricultural Experiment Station of Mississippi State College, has been named acting president. He will serve until a successor to Dr. George Duke Humphrey, who will become president of the University of Wyoming, has been elected.

DR. RALPH E. MONTONNA, professor of chemical engineering at the University of Minnesota, has been made assistant dean of the Graduate School. He will retain his academic status as professor of chemical engineering and will continue to act as director of the Minnesota Institute of Research.

DR. CARL W. MUNSHOWER has been promoted to a full professorship and has been named chairman of the department of mathematics of Colgate University. He succeeds Dr. Herman T. R. Ande, who has requested that he be relieved of administrative work.

DR. VLADIMIR ROJANSKY has been appointed chairman of the department of physics of Union College to succeed the late Dr. Peter I. Wold. Since November, 1943, Dr. Rojansky has been on leave of absence as a consultant on special war projects in Washington and in England.

DR. HAROLD J. REED, research fellow of the Mellon Institute of Industrial Research, Pittsburgh, has been appointed associate professor of metallurgy at Pennsylvania State College.

DR. F. WOOD JONES, F.R.S., professor of anatomy at the University of Manchester, has been appointed the first Sir William H. Collins professor of human and comparative anatomy in the Royal College of Surgeons of England.

IN the issue of SCIENCE for July 13 it is stated that Drs. Paul B. Hamilton and C. Arthur Knight, Jr., had been promoted from the rank of assistant to the rank of associate member of the Rockefeller Institute for Medical Research. It should have been said that they had been promoted from the rank of assistant to the rank of associate.

DR. E. K. BOLTON and Dr. Arthur C. Cope have been appointed representatives of the American Chemical Society in the Division of Chemistry and Chemical Technology of the National Research Council for the period from June 30, 1945, to June 30, 1948. They take the place of Dr. Per K. Frolich and Dr. Paul D. Bartlett, whose terms expired this June.

DR. MOLLIE A. GEISS has been appointed professor of pathology at the Woman's Medical College of Pennsylvania to succeed Dr. Helen Ingleby, who resigned in June to accept the position of pathologist at the Jewish Hospital in Philadelphia. Dr. Geiss has been on the faculty of the Woman's Medical College since 1923 and associate professor of pathology since 1932.

PROFESSOR WILBUR C. NELSON, head of the department of aeronautical engineering at Iowa State College, is spending the summer at the Aerodynamical Research Laboratory in Silver Spring, Md., of the Johns Hopkins University, where he is experimenting with air resistance of high-speed airships. Professor John M. Coan is acting head of the department during the summer.

DR. ROBERT S. JUSTICE joined at the end of June the scientific staff of Lakeside Laboratories, Inc., Milwaukee, in the capacity of pharmaceutical chemist.

DR. E. C. SANDEK has been appointed production manager of the Consumers Yeast Company of San Francisco.

D. N. WADIA has been elected president of the Council of the National Institute of Science of India for the year 1945. Professor S. P. Agharkar and Sir S. S. Bhatnagar have been elected vice-presidents.

IN the first ceremony of its kind, according to the *Journal* of the American Medical Association, two hundred and ninety-two recent medical and dental graduates of Harvard University, Tufts College and Boston University received army and navy commissions on June 23 in combined exercises in the Harvard Medical School Quadrangle. The Army commissions were awarded by Major General Sherman Miles, commanding the First Service Command, the Navy by Rear Admiral Felix Gyax, commandant of the First Naval District. Major General Norman T. Kirk, Surgeon General of the Army, gave the principal address. Other speakers were Dr. Leonard Carmichael, president of Tufts College, and Dr. James B. Conant, president of Harvard University. Dr. Daniel A. Marsh, president of Boston University, pointed out that the first combined exercises of the three schools of medicine demonstrated the spirit of cooperation in medical education.

A SYMPOSIUM on Mathematical Statistics and Probability will be held at the University of California at Berkeley from August 13 to 18. Speakers and chairmen will include Dean G. P. Adams, Professor E. M. Beesley, Professor B. A. Bernstein, Professor A. H. Copeland, G. B. Dantzig, Professor P. H. Daus, Professor J. L. Doob, Lieutenant Commander F. W. Dresch, Ph.D., Professor G. C. Evans, Professor Harold Hotelling, Professor P. L. Hsu, Professor J. H. McDonald, Professor A. H. Mowbray, Professor J. Neyman, Professor G. Polya, Professor Hans Reichenbach, Professor J. D. Tamarkin and Dr. Jacob Wolfowitz. Further information can be obtained by writing to the Statistical Laboratory, University of California, Berkeley 4, California.

THE National Research Council will act as adviser to the American Cancer Society in the proposed research program on the cancer problem. About a third of the five million dollars now being sought in the campaign of the society for funds will be devoted to research.

THE College of Medicine of the State University of Iowa, Iowa City, and the Iowa State Department of Health, in cooperation with the U. S. Public Health Service, will conduct at the State Hygienic Laboratory, Iowa City, from July 23 to 28, a special laboratory course in malaria and other tropical diseases.

THE *Journal* of the American Dental Association states that a group of specialists in the field of nutrition will leave shortly on a mission to help the undernourished people of Italy. Issac Schour and Maury Massler, both of the College of Dentistry of the University of Illinois, will be members of the mission, which is sponsored by the Unitarian Service Committee and the Congregational Christian Service Committee and which will go to Italy under the auspices of the United States Relief and Rehabilitation Administration. It will establish scientific standards for all large-scale feeding programs by UNRRA in newly liberated and destitute areas.

SPECIAL ARTICLES

NUTRITIVE VALUE OF THE MEXICAN TORTILLA[1]

THE per capita consumption of corn in Mexico approximates 280 grams daily, but many persons of low economic status consume as much as 700 grams daily. Essentially all this corn is eaten as *tortillas*, the daily bread of Mexico.

Perez[2] has presented data on the mineral and protein content of *tortilla*. Zozaya and Alvarado[3] have reported that a sample of *tortilla* contained no riboflavin, while samples of yellow corn and of white corn contained 0.21 mg and 0.20 mg, respectively. They did not indicate whether one of these corns was used in making the *tortillas* analyzed. A complete study of the nutritive value of *tortillas* has not been reported.

The preparation of *tortillas* has been described by Illescas.[4] One part of corn is placed in two parts of approximately 1 per cent. lime solution, heated to about 80° C for 20 to 45 minutes, then allowed to stand until the following day. Boiling is avoided, for this would produce a *masa* which adheres to the

[1] This study was conducted by the Nutritional Biochemistry Laboratories of the Massachusetts Institute of Technology, in collaboration with the Mexican Institute of Nutrition and the Rockefeller Foundation, under the auspices of the Pan American Sanitary Bureau and with the financial support of the W. K. Kellogg Foundation.

[2] M. Perez y Perez, "Contribucion al Estudio de algunos de los alimentos Mexicanos." Thesis, National University of Mexico, 1943.

[3] J. Zozaya and F. Alvarado R., Revista del Inst. Salubridad Enfermedades Tropicales, 4: 215, 1943.

[4] R. Illescas, *Soc. Mex. Hist. Nat.*, IV: 129–134, 1943.

hands and to the *comal* during cooking. On the next day the mother liquor is decanted from the corn (*nixtamal*), which is then washed two or three times with water. The *nixtamal* is ground by hand on a stone *metate* into a fine *masa*. In the larger towns the *nixtamal* is often taken to a power-driven mill for grinding, while in the cities the finished *masa* is purchased in the market.

About 50 grams of the *masa* are used to form round cakes, 15 to 20 cm in diameter and approximately 0.2 cm thick. These cakes are cooked on a *comal* (hot iron plate) for about 30 seconds, turned and cooked for 75 to 100 seconds. When it swells and becomes orange in color, the cake is turned again and cooked for another 30 seconds, when the *tortilla* curls to resemble a biconvex lens.

While people in the United States enjoy *tortillas* cooked to a hard brown cake, the Mexican removes the *tortilla* from the hot plate before it has browned and while it is still pliable. He often curls the *tortilla* and uses it as a spoon, biting off a portion with each mouthful. Frequently, the *tortilla* is rolled around a mixture of meat and chile, meat and bean or *mole* to form a *taco*.

In this study samples of corn, *nixtamal* and *masa* were obtained from small commercial mills (*molinos*) in various parts of Mexico City. In each instance the *nixtamal* and *masa* were prepared from the same supply of corn. The *masas* were taken to bakeries (*tortillerias*) adjacent to the mills and made into *tortillas* in the usual manner. In each case, a portion of the original corn, of *nixtamal*, of *masa* and of *tortilla* was taken, frozen in carbon dioxide ice, kept frozen during transit by air and until analyzed in Cambridge within five days after collection. It had been demonstrated previously that there was no measurable loss in the vitamin content of similar foods when shipped and stored in this manner. One series with yellow corn and two series with white corn were analyzed.

Samples were prepared for analysis by grinding in an electric mill. Carotene was measured by the adsorption technique of Moore,[5] thiamine fluorometri-

[5] L. A. Moore, *Indust. Eng. Chem. Anal. Ed.*, 12: 726, 1940.

TABLE 1

NUTRIENT CONTENT DURING PREPARATION OF MEXICAN TORTILLA

	Sample[1]	Corn		*Nixtamal*		*Masa*		*Tortilla*	
		Wet basis	Dry basis	Wet basis	Dry basis	Wet basis	Dry basis	Wet basis	Dry basis
Moisture (in per cent.)	*a*	15.0	0.0	45.5	0.0	51.9	0.0	38.9	0.0
	b	13.3	0.0	43.5	0.0	53.7	0.0	43.7	0.0
	c	13.0	0.0	37.8	0.0	55.4	0.0	43.2	0.0
	Ave.	13.8	0.0	42.3	0.0	53.7	0.0	41.9	0.0
Nitrogen (in per cent.)	*a*	1.19	1.40	0.74	1.36	0.65	1.35	0.84	1.37
	b	1.34	1.55	0.98	1.73	0.71	1.53	0.92	1.63
	c	1.47	1.69	1.29	2.07	0.75	1.68	1.03	1.81
	Ave.	1.33	1.55	1.00	1.72	0.70	1.52	0.93	1.60
Ash (in per cent.)	*a*	1.17	1.38	0.92	1.69	0.81	1.69	1.03	1.69
	b	1.30	1.50	0.86	1.52	0.72	1.55	0.87	1.55
	c	1.21	1.39	0.91	1.46	0.68	1.52	0.88	1.55
	Ave.	1.23	1.42	0.90	1.56	0.74	1.59	0.93	1.60
Calcium (mgs. per cent.)	*a*	8.	9.	120.	220.	108.	224.	131.	214.
	b	7.	8.	83.	147.	82	176.	101.	179.
	c	9.	10.	87.	139.	75.	169.	101.	178.
	Ave.	8.	9.	97.	169.	88.	190.	111.	190.
Phosphorus (mgs. per cent.)	*a*	242.	285.	180.	330.	154.	320.	195.	320.
	b	246.	284.	154.	272.	136.	294.	178.	316.
	c	222.	257.	174.	280.	135.	302.	178.	314.
	Ave.	233.	275.	169.	294.	142.	305.	184.	317.
Iron (mgs. per cent.)	*a*	3.2	3.8	2.1	3.9	2.1	4.2	2.8	4.5
	b	1.7	2.0	1.7	3.0	1.6	3.5	1.8	3.2
	c	1.9	2.2	1.9	3.0	1.4	3.1	1.9	3.3
	Ave.	2.3	2.7	1.9	3.3	1.7	3.6	2.2	3.7
Carotene (mgs. per cent.)	*a*	0.45	0.53	0.24	0.44	0.21	0.44	0.19	0.31
	b	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
	c	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
	Ave.[2]	0.15	0.18	0.08	0.15	0.07	0.15	0.06	0.10
Thiamine (mgs. per cent.)	*a*	0.38	0.44	0.21	0.39	0.19	0.39	0.18	0.29
	b	0.32	0.37	0.20	0.35	0.17	0.37	0.19	0.34
	c	0.32	0.37	0.20	0.32	0.16	0.36	0.21	0.37
	Ave.	0.34	0.39	0.20	0.35	0.17	0.37	0.19	0.33
Riboflavin (mgs. per cent.)	*a*	0.08	0.09	0.05	0.09	0.05	0.10	0.05	0.08
	b	0.08	0.09	0.06	0.11	0.04	0.09	0.06	0.11
	c	0.08	0.09	0.06	0.10	0.05	0.11	0.07	0.12
	Ave.	0.08	0.09	0.06	0.10	0.05	0.10	0.06	0.10
Niacin (mgs. per cent.)	*a*	1.55	1.82	0.80	1.47	0.70	1.46	0.89	1.46
	b	1.68	1.94	1.18	2.09	0.83	1.79	0.93	1.65
	c	1.70	1.95	1.15	1.85	0.85	1.90	1.07	1.89
	Ave.	1.64	1.90	1.04	1.80	0.79	1.72	0.96	1.67

[1] Sample *a* was yellow corn, *b* and *c* were white corn.
[2] Since white corn contained no measurable carotene, these averages may be insignificant.

cally according to Hennessy,[6] riboflavin fluorometrically according to Andrews,[7] niacin microbiologically according to the U. S. Pharmacopoeia,[8] phosphorus spectrophotometrically according to Fiske and SubbaRow,[9] iron spectrophotometrically according to Koenig and Johnson,[10] while water, ash, nitrogen and calcium were estimated using the procedures of the A.O.A.C.[11] The analytical results are presented in Table 1 on a wet basis; also, they have been calculated to the dry basis to allow direct comparison.

The carotene content of the white corns was too low for measurement. There was a 40 per cent. loss in the carotene of the yellow corn during the preparation of the *nixtamal* and the *tortillas*. The losses in thiamine and niacin were relatively small. No measurable loss in riboflavin was noted. The calcium content increased 2010 per cent., the phosphorus content 15 per cent., and the iron content 37 per cent. The high calcium content of the *tortilla* resulted from treatment of the corn with lime water. The Mexican has achieved an adequate calcium intake by this food practise, for an average daily consumption of 280 grams of *tortilla* furnishes more than 500 mgs of calcium.

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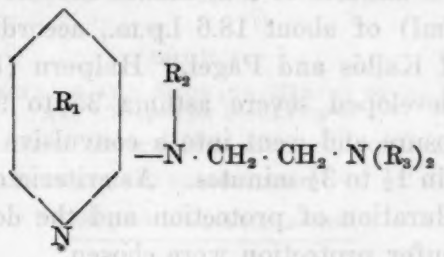
ANTIHISTAMINIC AND ANTIANAPHYLACTIC ACTIVITY OF SOME α-PYRIDINO-ETHYLENEDIAMINES

BOVET and Staub[1] and Staub[2, 3] described the antihistaminic and antianaphylactic activity of thymoxyethyldiethylamine (929 F), (*I*) and N,N-diethyl-N¹-ethyl-N¹phenylethylenediamine (1571 F), (*II*). The specific activities of substance *I* have been confirmed in this country by different authors[4–9]. Both substances are, however, too toxic to be used in man.

In 1942 Halpern[10] studied certain homologues of Substance *II* and observed that N¹phenyl-N¹ethyl-N-dimethylethylenediamine (*III*) and N¹phenyl-N¹benzyl-N-dimethylethylenediamine (*IV*) were much more active and much better tolerated. Clinical reports[11, 12] confirm the effectiveness of Substance *IV* in various allergic diseases.

In searching for more active substances, a series of compounds have been prepared, especially pyridine derivatives of the general formula:



The biological activities of the new compounds have been tested on the isolated intestinal strip of the guinea pig by adding them to the bath liquid one minute before the standard dose of 1 γ histamine was given, or after the histamine contraction had fully

TABLE 1
COMPARATIVE ACTIVITY IN VITRO

Compound No.	R₁	R₂	R₃	Activity*
63	pyridyl	benzyl	methyl	0.02 γ
67	"	"	ethyl	> 5 γ
52	"	phenyl	methyl	> 5 γ
76	"	"	ethyl	> 10 γ
82	"	isopropyl	methyl	> 10 γ
77	"	propyl	ethyl	> 10 γ
84	"	β-pyridyl	methyl	> 10 γ
75	"	α-pyridyl	ethyl	> 10 γ
74	β-picolinyl	benzyl	methyl	2 γ
91	α¹-picolinyl	"	"	1 γ
106	γ-picolinyl	"	"	0.2 γ

* The activity is expressed in γ per ml of bath liquid capable of neutralizing 1γ/ml of histamine diphosphate.

[1] D. Bovet and A. M. Staub, *C. R. Soc. Biol.*, 124: 547, 1937.
[2] A. M. Staub and D. Bovet, *ibid.*, 125: 818, 1937.
[3] A. M. Staub, *Ann. Inst. Pasteur*, 63: 400 and 485, 1939.
[4] S. R. Rosenthal and M. L. Brown, *Jour. Immunol.*, 38: 259, 1940.
[5] D. Minard and S. R. Rosenthal, *Proc. Soc. Exp. Biol. Med.*, 44: 237, 1940.
[6] G. A. Mc. Vicar and E. W. McHenry, *Canad. Med. Asn. Jour.*, 44: 80, 1941.
[7] H. B. Wilcox, Jr., and B. C. Seegal, *Jour. Immunol.*, 44: 219, 1942.
[8] J. E. Bourque and E. R. Loew, *ibid.*, 138: 341, 1943.
[9] G. A. Hallenbeck, *Am. Jour. Physiol.*, 139: 329, 1943.
[10] B. N. Halpern, *Arch. Intern. Pharmacodyn.*, 68: 339, 1942.
[11] Ph. Decourt, *Presse Med.*, 50: 773, 1943.
[12] J. L. Parrot, *ibid.*, 50: 771, 1942.

developed. Both methods yielded essentially the same results as shown in Table 1.

Secondary amines all have been found to be inactive or almost inactive by contrast to the above pyridine derivatives, which are tertiary amines.

Doses of from 0.001 to 0.01 γ/ml of Compound 63 were active; 0.02 γ/ml prevented any response of the intestinal strip to histamine diphosphate in doses of from 0.2 to 1.0 γ/ml, or restored normal tonus when given after histamine. To abolish or prevent an acetylcholine contraction with Compound 63 a dose one hundred times greater is necessary in contrast to an antispasmodic like Trasentine, which is one hundred times more active against acetylcholine than against histamine.

The activity *in vivo* was tested in guinea pigs exposed for 5 minutes to a histamine-aerosol-air-stream (0.139 γ/ml) of about 18.6 l.p.m., according to the method of Kallós and Pagel,[13] Halpern (*l.c.*). Our animals developed severe asthma 35 to 90 seconds after exposure and went into a convulsive shock-like condition in 1½ to 3½ minutes. As criteria of activity, both the duration of protection and the doses necessary to confer protection were chosen.

In this test, repeated at hourly intervals, appearance of convulsions could be delayed in most animals from 2 to 6 hours if the animals were treated 15 minutes before the first exposure by 0.1 mg/kg of Compound 63.

Compound 63 was about twice as active as Compound *IV* and ten times more active than Compound 106, and one hundred times more active than Compound 74. 0.1 mg/kg of Compound 63 administered subcutaneously fifteen minutes before exposure protected the majority of animals for two to six hours from developing convulsions. The activity by mouth of the same compound was only slightly less pronounced than by subcutaneous injection. A group of typical experiments is shown in Table 2.

TABLE 2

HISTAMINE SHOCK—NUMBER OF ANIMALS PROTECTED BY DIFFERENT DOSES OF N,N-DIMETHYL-N¹-BENZYL-N¹-(α PYRIDYL) ETHYLENEDIAMINE HCL FOR 0 TO OVER 6 HOURS

Mg/kg	Hours of protection								Total number animals used
	0	0–1	1–2	2–3	3–4	4–5	5–6	over 6	
0.1	2	3	5	5	2		1	4	22
0.2		1	1		1	4	3		10
0.5	1	4	2	3	3	7	4		24
1.0		1		1	1	7	6	7	23
5.0					3	9	10	15	37
10.0							8	2	10
									(126)

Guinea pigs sensitized with horse serum in the customary way were treated subcutaneously with antihistaminic substances 21 days later, and 10 minutes before they received an intracardial injection of 0.5 ml horse serum. The smallest dose of Compound 63 which protected guinea pigs from acute anaphylactic shock was 0.1 mg/kg. Table 3 shows the effect of

TABLE 3

ANAPHYLACTIC SERUM SHOCK IN GUINEA PIGS—PROTECTION WITH 63

#	Dose 63 mg/kg	Serum re-injection	Death
1	None	Shock in 1 min.	In 2 mins.
2	None	" " " "	" " "
3	0.1	" " " "	" 24 hours
4	0.1	No shock, weak after 10 min.	Survived
5	0.5	" "	"
6	0.5	" ", convulsions after 15 mins.	In 24 hours
7	0.5	" "	Survived
8	1.0	" ", weak after 25 mins.	"
9	1.0	" "	"
10	1.0	" "	"
11	1.0	" "	"
12	1.0	" "	"

various dosages, and demonstrates that with 1.0 mg/kg complete protection is obtained. In these experiments also, Compound 63 was about twice as active as the corresponding phenyl compound *IV*.

The conclusion is reached that a close relationship exists between the antihistaminic activity demonstrated *in vitro* and *in vivo* and the antianaphylactic property of Compound 63. Reports on other pharmacological activities of Compound 63 are in press, and a study on the tolerance and therapeutic activity in patients suffering from allergic diseases is under way.

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THE ROLE OF NICOTINE IN THE CIGARETTE HABIT

THE physiological and psychological basis for the tobacco habit has been the subject of considerable speculation. Variously suggested factors include the following: nicotine; optical perception of the smoke; fire worship; agreeable smell and taste; mechanical manipulation of cigar or cigarette somewhat resembling the influence of the nipple on the infant; pleasurable irritation of the laryngeal and tracheal sensory branches of the pneumogastric nerve; relief of tension; stimulation; sociability; gives people something to do; permits one to do nothing, gracefully; produces a rise in blood sugar; satisfies a desire or craving; one becomes used to combatting with nicotine hunger and thirst, joy and pain, heat and cold, irritation and languidness.

[13] P. Kallós and W. Pagel, *Act. Med. Scandiv.*, 91: 292, 1937.

To prove or disprove or even to debate the merits of each of these suggestions individually is quite beyond the scope of our intentions, and we simply wish to record some observations that we have made on the role of nicotine in the cigarette habit.

Of particular interest in this connection are the recent observations of Johnston[1] on the comparison of the effects of smoking with those of hypodermically injected nicotine. Whereas smokers almost invariably thought the sensation (following nicotine injection) pleasant and, given an adequate dose, were disinclined for a smoke for some time thereafter, non-smokers usually termed it "queer." Johnston gave himself 80 hypodermic doses of nicotine at the rate of 3 to 4 a day with some smoking; after this course he preferred a hypodermic injection of 1.3 mg of nicotine to inhaling a cigarette, and feelings of deprivation were experienced when the injections were discontinued.

Recently we have had the opportunity to make observations on the role of nicotine in the tobacco smoking habit, using a somewhat different approach. Having been furnished with an adequate amount of tobacco naturally low in nicotine,[2] the tobacco was divided into two lots. One lot was treated with sufficient nicotine in the form of nicotine malate to give a final nicotine content of about 2 per cent. A casing solution consisting of 3.5 pounds of glycerine and 2.4 pounds of invert sugar per 100 pounds of tobacco was then sprayed on each lot following which each lot was made into cigarettes. Subsequent analysis for nicotine with silicotungstic acid according to the A.O.A.C.[3] showed that the low nicotine cigarettes contained 0.23 per cent. nicotine, the cigarettes to which nicotine had been added 2.08 per cent. nicotine. Smoke from these cigarettes collected by the procedure described by Bradford, Harlan and Hanmer[4] and analyzed for nicotine by the silicotungstic acid method assayed 0.34 mg nicotine per cigarette for the low nicotine cigarettes and 1.96 mg per cigarette for the ones to which nicotine had been added.

Twenty-four habitual cigarette smokers (all inhalers) ranging in age from 22 to 50 years were selected, each of whom felt that he could not easily forego the habit. Throughout the experiment each subject kept a daily record of the number of cigarettes smoked. For the first month, the subjects smoked their accustomed brands in order that a record of their normal smoking habits might be obtained. Following this each was given to smoke at least 2 cartons of the cigarettes to which nicotine had been added, followed by at least 4 cartons of low nicotine cigarettes, and these in turn were followed by 2 cartons of the cigarettes containing added nicotine. This use of the experimental cigarettes to which nicotine had been added was made necessary by the fact that the smoking quality of the low nicotine tobacco was decidedly inferior to that of standard cigarettes. By this means it was felt that a control on the taste and aroma factors was obtained. In other words, by the time the subject was suddenly virtually deprived of nicotine, he was fairly well accustomed to the inherently different taste and aroma of the low nicotine tobacco. The subjects were asked to keep a personal account, and in addition were repeatedly questioned as to their reactions to each carton smoked. In no instance did they know in advance when switches in nicotine content were made. The results are expressed in Table 1.

TABLE 1

ROLE OF NICOTINE IN THE SMOKING HABITS OF 24 INVETERATE CIGARETTE SMOKERS

Subject	Average daily consumption: Standard brands	Experimental cigarettes: Nicotine added (first period)	Low nicotine	Nicotine added (second period)	Degree to which nicotine was missed	
L.H.	21.8	21.4	21.9	22.5		0
R.M.	20.7	24.2	31.5	20.3		0
S.N.	20.4	20.6	19.8	20.5		0
H.S.	*ca.* 60	*ca.* 60	*ca.* 75	*ca.* 60		0
J.B.	19.2	14.8	17.4	16.1		0
N.C.	19.4	18.9	20.1	21.3		0
(Means)	26.9	26.6	30.9	26.8	(Total)	6
A.F.	24.0	23.8	22.3	18.9		+
S.H.	21.3	20.8	24.5	25.6		+
J.M.	19.3	19.1	36.2	23.9		+
G.O.	20.8	20.3	23.4	19.7		+
F.W.	25.4	19.1	30.2	28.5		+
H.W.	23.4	28.9	22.7	26.6		+
(Means)	22.4	22.0	26.5	23.9	(Total)	6
J.F.	28.2	38.2	32.4	37.5		++
P.L.	24.5	27.2	28.5	23.1		++
F.P.	18.2	19.5	25.0	22.2		++
(Means)	23.6	28.3	28.6	27.6	(Total)	3
G.B.	25.5	17.0	27.7	20.7		+++
E.H.	22.1	25.5	28.5	30.3		+++
K.K.	25.1	27.3	26.4	27.4		+++
H.B.	25.3	28.4	25.8	24.2		+++
M.F.	21.4	25.8	24.8	28.6		+++
D.G.	34.4	27.6	27.0	26.7		+++
F.H.	28.8	24.4	26.7	25.4		+++
W.P.	21.0	21.6	16.1	19.3		+++
C.Z.	21.2	24.8	18.6	21.3		+++
(Means)	25.0	24.7	24.6	24.9	(Total)	9

0 Did not miss the nicotine.
+ Mild initial dissatisfaction with low nicotine cigarettes.
++ Definite temporary lack of satisfaction with low nicotine cigarettes.
+++ Definite and prolonged lack of satisfaction with low nicotine cigarettes.

Six of the 24 subjects experienced no change in physical or mental tranquility during their period on low nicotine cigarettes; 6 experienced an initial vague lack in the satisfaction that they normally derived

[1] L. M. Johnston, *Lancet*, 2: 742, 1942.
[2] Through the courtesy of Dr. W. D. Valleau, Kentucky Agricultural Station, Lexington, Ky.
[3] Assoc. Official Agr. Chem., "Official and Tentative Methods of Analysis," 5th ed., p. 64, 1940.
[4] J. Bradford, W. Harlan and H. R. Hanmer, *Indust. and Eng. Chem.*, 28: 836, 1936.

from smoking; 3 definitely missed the nicotine but became adapted to the change in one to two weeks; 9 definitely missed the nicotine and continued to do so throughout the period (approximately 1 month). The symptoms experienced by the latter 2 groups for the most part took the form of varying degrees of heightened irritableness, decreased ability to concentrate on mental tasks, feeling of inner hunger or emptiness, hypoesthesia (1 case), in short, virtually the same symptoms experienced by many individuals on stopping smoking. Some of the individuals in the last group "just could not take it" and admitted to interspersing a few cigarettes of ordinary nicotine content during their period on low nicotine cigarettes.

Conclusions

It would seem clear from these results that with many individuals nicotine becomes a major factor in their cigarette habit. Equally certain, with many individuals nicotine is not a factor in their cigarette habit. Even in those individuals in whom nicotine has become a major factor we feel that a cigarette containing no nicotine would be grudgingly accepted as better than no cigarette at all.

There is seemingly no correlation between the number of cigarettes smoked daily and the degree to which nicotine becomes a factor. Indicative of this is the heaviest smoker in the series, a man who for many years has smoked 3 packages daily. This individual made the switch to low nicotine cigarettes without the slightest difficulty.

Groupings on the basis of subject age or duration of the habit showed no correlation with the degree to which nicotine was missed. However, the number of subjects involved was too small to arrive at any definite conclusions in these respects.

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PENICILLIN IN EXPERIMENTAL SPOTTED FEVER

Until relatively recently the treatment of spotted fever (Rocky Mountain spotted fever) has been purely supportive and symptomatic. Published reports on chemotherapeutic treatment are scant. In 1938 Baker reported that the intravenous administration of neoarsphenamine in metaphen solution was beneficial in relieving symptoms and, in a later publication, that all treated cases had survived.[1, 2] The number of cases was not stated. No doubt the sulfonamides have been given in many instances not reported in the literature. In infected guinea pigs the use of sulfapyridine and prontosil resulted in no improvement,[3] and Topping concluded that there was evidence of their being harmful and that they should not be used. We have confirmed and extended these observations, studying the effect of sulfamerizine, sulfadiazine, sulfapyridine and sulfathiazole.[4] In our hands, the latter two drugs were very definitely contraindicated, deaths occurring in the treated animals sooner than in the controls. The first two drugs were without effect. Steinhaus and Parker,[5] in addition to testing some of the sulfonamides, treated guinea pigs with atabrine and tyrothricin and concluded that none of the substances used was of any value. Serotherapy (rabbit immune globulin) is coming into wider use,[6] but it will take some years to evaluate the benefit of this form of treatment in human spotted fever where the mortality with supportive treatment alone is only about 20 per cent. Its striking effects in guinea pigs, however, even when very small quantities are employed,[4] tend to make one exceedingly enthusiastic about its use in the human disease.

In view of the extraordinary effectiveness of penicillin in many other infectious diseases, it seemed pertinent to study its effects on experimental spotted fever. Its use in man has been reported in one case diagnosed as spotted fever; the patient recovered.[7]

Male guinea pigs weighing from 450 to 600 grams were infected by the intraperitoneal route with 1 cc of a 10 per cent. suspension of spleens obtained from guinea pigs infected with the Bitter Root strain of spotted fever. Temperatures were taken twice daily to determine exactly the time of onset of fever. In the first experiment, groups of 4 guinea pigs were selected for treatment 24, 48, 72 and 96 hours after the temperatures rose above 103.5° F. All guinea pigs, except the 96-hour group, received intramuscularly 200 Oxford units of penicillin contained in a volume of 0.2 cc every 4 hours for 36 hours, or a total of 1,800 units per animal. The disease in the guinea pigs selected for treatment 96 hours after the onset of fever had progressed so far that it was deemed advisable to give them larger doses. Five hundred units at 4-hour intervals were administered for 36 hours, or a total of 4,500 units per guinea pig. No beneficial effect could be observed in any of the treated animals.

A second experiment was undertaken to see if the larger dose of penicillin given earlier in the disease

[1] G. E. Baker, *Rocky Mt. Med. Jour.*, 35: 36, 1938.
[2] *Idem, Ann. Intern. Med.*, 17: 247, 1942.
[3] N. H. Topping, *U. S. Pub. Health Rep.*, 54: 1163, 1939.
[4] Unpublished experiments.
[5] E. A. Steinhaus and R. R. Parker, *U. S. Pub. Health Rep.*, 58: 351, 1943.
[6] N. H. Topping, *U. S. Pub. Health Rep.*, 58: 757, 1943.
[7] P. K. Edmunds, *Rocky Mt. Med. Jour.*, 41: 910, 1944.

and over a longer period of time would produce better results. Six guinea pigs approximately 500 grams in weight were given 500 units of penicillin intramuscularly every 4 hours, the initial injection being given 48 hours after the first elevation of temperature. Treatment was continued for 4 days, a total of 12,000 units being administered per guinea pig (the equivalent of about 2 million units for an adult weighing 160 pounds). Six other animals received one injection of 1 cc of spotted fever rabbit immune globulin intraperitoneally 48 hours after the onset of fever. Sixteen untreated guinea pigs served as controls. The results are summarized in Table 1.

TABLE 1

No. of guinea pigs	Treatment	Result
6	500 units penicillin every 4 hours for 4 days. Total 12,000 units per animal	6 died
6	1 cc spotted fever rabbit immune globulin	6 recovered
16	None—Controls	8 died 8 recovered

It will be seen that all the animals receiving the penicillin succumbed to the disease. The treatment had no beneficial effect on any of the signs and symptoms characteristic of this strain of spotted fever, *i.e.*, loss of appetite, loss of weight, sustained high temperature, scrotal involvement, etc. Smears of spleen and lung at autopsy showed rickettsiae to be as numerous as in the untreated controls. In the globulin-treated animals, on the other hand, the progress of the disease was arrested. The scrotal swelling subsided in about 2 days, whereas in most of the controls and in the guinea pigs treated with penicillin the lesion progressed to petechial hemorrhages, adhesions of the tunica vaginalis and finally necrosis.

Studies of plasma levels showed that the dosage and time schedule employed in the second experiment should have been adequate for treatment. Three male guinea pigs weighing 510 to 525 grams were given 500 units of penicillin into the muscles of the leg. Plasma was obtained 30 minutes and 4 hours after the injection, and the drug levels determined by the Rammelkamp method,[8, 9] These are recorded in Table 2.

TABLE 2

Guinea pig no.	Units of penicillin per cc of plasma	
	30 minutes after drug	4 hours after drug
1	0.25	0.03
2	0.12	0.02
3	0.19	0.03

It will be noted that absorption of penicillin in the guinea pig was very rapid following intramuscular injection and that even after a lapse of 4 hours detectable quantities of the drug were still present.

SUMMARY

Guinea pigs infected with a virulent strain of spotted fever received large doses of penicillin intramuscularly every 4 hours. The injections were begun 48 hours after the onset of fever. Controls included untreated animals and others that received one dose of spotted fever rabbit immune globulin. The penicillin had no effect on the classic symptoms of this disease and all the treated animals died. (The toxicity of penicillin for guinea pigs probably was a contributing factor.)[10, 11] Eight out of 16 controls died; all guinea pigs receiving globulin survived. Penicillin plasma determinations led to the belief that the treatment was adequate to bring about recovery had the agent been of any value.

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SCIENTIFIC APPARATUS AND LABORATORY METHODS

THE USE OF "TAGGED" DERIVATIVES IN THE FLUORIMETRIC ASSAY OF VITAMINS[1]

THIS preliminary note is the first of a series of papers dealing with the application of fluorimetry to the assay of vitamins of the B-complex. At present, such methods are used only in the case of riboflavin and thiamin; in the first instance, the fluorescence of the vitamin itself, and in the second instance, that of an oxidation product, thiochrome, is measured. In this communication, we present a new principle in fluorimetric vitamin assay methods, the use of "tagged" derivatives. By this means, the presence of a relatively light-insensitive compound may be determined quantitatively through the preparation of a highly fluorescent derivative. Extracts of biological materials, if properly prepared, contain relatively few fluorescent substances, and most of the latter give emissions in ultraviolet light. Those which fluoresce in ultraviolet light, including the reagents which are

[1] This study was aided by the Clara A. Abbott Fund of Northwestern University, Chicago.

[8] We are indebted to R. McC. Woodward, of the Department of Bacteriology, Medical Research Division, for the penicillin assays.

[9] C. H. Rammelkamp, *Proc. Soc. Exp. Biol. and Med.*, 51: 95, 1942.

[10] D. M. Hamre, G. Rake, C. M. McKee and H. B. MacPhillany, *Am. Jour. Med. Sci.*, 206: 642, 1943.

[11] H. Pinkerton, Personal communication.

added, rarely exhibit this property at the higher wave-lengths of visible violet light. Therefore, the method attains considerable specificity if "tagged" derivatives are prepared which fluoresce in light of approximately 440 millimicrons wave-length. We have applied these principles successfully to the determination of nicotinic acid and p-aminobenzoic acid, using the König reaction.

In 1904, König[2] and Zincke[3] described reactions in which the very stable pyridine molecule, by combining with CNBr, 2,4-dinitrophenyl chloride, or similarly reactive reagents, formed relatively unstable pyridinium compounds which yielded highly colored crystalline derivatives of glutaconic dialdehyde on further reaction with aromatic amines. These reactions have since been adapted to minute quantities of nicotinic acid, and they form the basis of all present methods for the colorimetric determination of the vitamin.

König found that many of the derivatives possessed desirable properties as dyes, and he noted that the dyed fabrics had a fluorescent sheen in bright light. Although the reaction was subsequently studied in great detail by König,[4] Zincke[5] and others,[6] no mention of the fluorescent properties[7] of the dyes was made, as far as we are aware, except in the first communication by König.

In a study of the conditions for the maximum production of fluorescent derivatives, it was found that the intermediate N^1-cyanbromo nicotinic acid fluoresced markedly in ultraviolet light. Many of the amines which were tested and the guanidine derivatives[8,9] which are produced by the reaction of the excess of CNBr and amine in the solution gave varying intensities of fluorescence in ultraviolet light. However, these substances gave negligible fluorescence when a primary violet filter, having a maximum transmission at approximately 440 millimicrons (Corning filters 511 and 038), and a secondary orange-colored filter (Corning filter 351) were used. This filter system is commonly used in the determination of riboflavin. Under the latter conditions, many of the glutaconic dialdehyde derivatives in aqueous solution gave a greenish-yellow fluorescence similar to that of riboflavin.

The structure of the amine used in the reaction and a final high acidity of HCl are very important. Relatively little or no response in violet light was seen when the reaction was carried out with various amines as in the procedure of Melnick and Field.[10] Perhaps for this reason the phenomenon has been overlooked. However, when HCl was added, either with the aromatic amine or after the latter had reacted with the intermediate pyridinium compound, then a marked fluorescence was obtained with certain of the amines. The maximum effect was obtained at acidities above 0.5 *N* HCl. Polar radicals, especially when substituted in the para-position in the aniline molecule, conferred fluorescent properties on the dialdehyde derivative. The radicals, from the least to the most effective, may be placed in the following approximate order: H, CH_3, OCH_3, Cl, NH_2, OH, SO_3H, COOH, $COCH_3$. Thus p-aminobenzoic acid and p-aminoacetophenone, particularly the latter, yielded highly fluorescing derivatives.

The following procedure is suggested for the determination of nicotinic acid in suitably prepared extracts. Transfer 5.0 cc volumes of extract, containing from 1 to 6 micrograms of nicotinic acid, to two cork-stoppered colorimeter tubes, A and B. Warm the tubes and contents 5 to 10 minutes in a water bath which is maintained at $50 \pm 2°$ C. To tube A add *from a burette* 2.0 cc of 0.5 *M CNBr* in 5 per cent. KH_2PO_4. To tube B, the "amine blank," add 2.0 cc of 5 per cent. solution of KH_2PO_4. Return both tubes immediately to the water bath and incubate for a period of exactly 10 minutes. Cool the tubes 5 to 10 minutes in a water bath at approximately 25° C. Now add 3.0 cc of a freshly prepared 5 per cent. solution of p-aminoacetophenone in 2 *N* HCl. Protect the tubes from strong light. Depending upon the temperature of the room and the reagents, the maximum fluorescence will be attained in 30 to 45 minutes; it remains constant for 15 minutes, and then declines slowly. Readings should, therefore, be made 30 and 45 minutes after addition of the amine reagent.

Some types of sample may contain cyanogen bromide-reacting substances. For such samples it is necessary to prepare two additional tubes, C and D. To tube C, the "CNBr blank," add 2.0 cc of CNBr reagent *from the burette,* and 3.0 cc of 2 *N* HCl. To tube D, the "color blank," add 2.0 cc of 5 per cent. KH_2PO_4 solution and 3.0 cc of 2 *N* HCl. The conditions of incubation are the same as for tubes A and B. The corrected reading then is: A – (B + C – D).

Because of the strong absorption of the violet light by the yellow glutaconic dialdehyde derivatives, the relation between fluorescence and concentration of the vitamin is no longer linear when more than 6 micrograms are assayed. With such small quantities,

[2] W. König, *Jour. prakt. Chem.*, 70: 1, 1904.
[3] T. Zincke, *Annalen d. Chemie,* 330: 361, 1904.
[4] W. König and R. Bayer, *Jour. prakt. Chem.*, 83: 325, 1911.
[5] T. Zincke and coworkers, *Annalen d. Chemie,* 333: 296, 1904; 338: 107, 1905; 339: 193, 1905; 341: 365, 1905; 353: 380, 1907.
[6] F. Reitzenstein and W. Bruening, *Jour. prakt. Chem.*, 83: 97, 1911.
[7] Zincke observed marked dichroism of solutions of the crystalline derivatives.
[8] A. W. Hoffman, *Annalen d. Chemie,* 67: 129, 1848.
[9] W. König, *Jour. prakt. Chem.*, 69: 1, 1904.
[10] D. Melnick and H. Field, Jr., *Jour. Biol. Chem.*, 134: 1, 1940.

a sensitive instrument, such as the Coleman photofluorometer, Model 12, must be used.

By means of an apparatus which was developed three years ago by Mr. George S. Liebeck, of the American Telephone and Telegraph Company, and which has been in constant use since, from 0.1 to 6 microgram quantities in 5 cc of extract can be determined. This range is made possible by very high stable electronic amplification and a variable shunt which increases or decreases the sensitivity of the microammeter with which the readings are obtained. At one-half of the maximum sensitivity of the instrument, 0.1 to 1.0 micrograms in 5 cc of standard solution, at increments of 0.1 micrograms, gave the following corrected (blank, 1.6) galvanometer deflections: 2.9, 5.9, 8.2, 10.1, 13.1, 17.3, 19.2, 22.7, 25.4, 29.5. One galvanometer deflection, therefore, indicated the presence of 0.0068 microgram of nicotinic acid per cc of extract.

The procedure has given results with wheat flours, cornmeal and animal and green plant tissues which generally check closely with those obtained by the microbiological method. The results by the latter method were obtained on acid digests. In a few instances, for example, with soybean meal, the fluorimetric method has given definitely higher results than the microbiological or colorimetric methods. This effect is not due to other fluorescent substances such as riboflavin, or amine-, or CNBr-reactive materials. It appears to be due to pyridine-like substances which react with *both* CNBr and the amine. Whether or not these substances belong in the category of physiologically active pyridine compounds studied by Elvehjem and coworkers[11] is now being determined in this laboratory.

The procedure and its application to biological materials will be described in detail in a later publication.

Summary: In a study of the König reaction, it was found that nicotinic acid, on reacting with CNBr and certain substituted aromatic amines, yields glutaconic dialdehyde derivatives which fluoresce with a greenish-yellow light in visible violet light of about 440 millimicrons wave-length. A procedure was described which is applicable to 0.1 to 6 micrograms in 5 cc of solution or extract. It is suggested that the principle of preparing fluorescing "tagged" derivatives be applied to other vitamins of the B-complex.

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[11] W. A. Krehl, C. A. Elvehjem and F. M. Strong, *Jour. Biol. Chem.*, 156: 13, 1944.

THE INHIBITION OF POLLEN PRODUCTION IN RAGWEED BY THE USE OF CHEMICAL SPRAYS[1]

DURING the course of a pollen survey, made for the Michigan Department of Health in the summers of 1940, 1941, 1942, and 1944, it became apparent that, while data in regard to the number of ragweed pollen grains in the air at any time are valuable to physicians working in the field of pollen allergy, there is a much more important problem in those regions where ragweed grows freely. The more fundamental problem is not the accumulation of numerical data concerning pollen incidence, but rather the development of some method of control for this menace to the health and well-being of many people.

A program designed to eradicate ragweed from large areas frequently faces some opposition because of the possibility that successful eradication of these plants may tend to increase soil erosion in certain regions and because the weeds have some value as cover and food for wild-life.

The ideal solution of this pollen problem would be the development of a method by which large areas may be treated with some agent which will prevent flower formation, or at least pollen production, and not destroy the vegetative portion of the offending plants. The chief obstacles to the use of chemicals for this purpose are the cost of materials and the possible danger to cultivated crops and livestock. Observations on weed control in vegetable crops by the use of selective herbicides, however, have shown that certain chemicals are available which are not a hazard to animal life and may be useful in this connection.

In the period of August 20 to September 16, 1944, a number of test sprayings were made on areas having a heavy growth of ragweed. Ragweed on these plots began pollinating the last week of August and spray treatments were begun as soon as pollen release was evident. All sprays were applied at 100 pounds pressure and at the rate of 100 gallons per acre.

RESULTS

G–412[2] (di-nitro-secondary-butyl-phenol) in kerosene gave a complete kill of ragweed within a period of six hours. The vegetative portion of the plant, as well as the flower spikes, turned brown, and pollen release was stopped. Water solutions of this material killed more slowly, and frequently killing was not complete.

G–410[2] (penta-chlor-phenol) gave a 75 per cent. kill in twelve hours, but some stems remained alive and continued growth until frost. Pollen was not again produced by these plants.

[1] Journal Article No. 755 (n.s.) from the Michigan Agricultural Experiment Station.
[2] Supplied by the Dow Chemical Company.

Sinox (in kerosene) killed only the younger leaves and flower spikes. Axillary buds developed and young flower shoots were evident at the time of frost.

Kerosene alone killed the younger leaves of ragweed and any flowers that were ready to open at the time of spraying, but the effect was temporary, and the plants recovered within a short time and continued to release pollen.

Discussion

These results indicate that it is possible to stop pollen production in ragweed with chemical sprays. Greenhouse tests and some field observations, however, indicate that most of the materials used in this series of tests are more or less toxic to cultivated crops at the concentrations used in these experiments. Very few crops will tolerate kerosene, and thus the method of weed control described would be of little value in areas where crops are being grown.

Recent reports of work with growth-regulating substances[3, 4] have shown that ragweed, as well as many other annual weeds, can be killed by spraying with "2–4–D" and other similar materials. Limited greenhouse tests, conducted during the winter, have shown that low concentrations of these substances have a very pronounced effect on ragweed. When young ragweed plants, six inches tall, were sprayed, growth of terminal buds was stopped. No further elongation occurred during the observation period of two months, nor were there any flower spikes evident. Leaves present at the time when sprayed remained green, and the older parts of the stem appeared normal.

Confirmation of these results will be sought as soon as plants are available under natural conditions. Details of concentration of "2–4–D" and time of application remain to be explored, but the information already available indicates that it will be possible to develop a program of treatment that will prevent the production of pollen by common ragweed without having the undesirable features of complete destruction of vegetation.

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[3] C. L. Hamner and H. B. Tukey, *Bot. Gaz.*, 106: 232–245, 1944.

[4] P. C. Marth and J. W. Mitchell, *Bot. Gaz.*, 106: 224–232, 1944.

DISCUSSION

THE CONTROVERSY ON CHOLINESTERASES

For about two years a controversy, in the form of articles and counter articles in Science, has continued between Mendel and Rudney and Alles and Hawes concerning claims of priority for the discovery of two separate enzymes capable of hydrolyzing choline esters on the one hand, and the use of the term "pseudo-cholinesterase" on the other. The former point should be resolved simply by referring to the facts, and the latter should be considered without delay since, if the term is disadvantageous, it ought to be dropped from the scientific literature as soon as possible. The writer, as a completely disinterested individual, relative to sides in the matter, has undertaken this objective discussion in the hope that it might help to clarify the controversial issues.

It would appear that the significant facts are as follows:

(1) Alles and Hawes[1] were the first to point out, by experiments on human blood, that two apparently distinct enzymes exist that are capable of hydrolyzing acetylcholine. They arrived at this conclusion, which was reiterated by Hawes and Alles,[2] on the basis of differences in the enzymatic properties of the blood cells and serum as regards activity-pH, activity-sodium chloride and activity-substrate concentration relationships, as well as the differences effected by introducing methyl groups into the choline portion of the substrate esters. These investigators found that, whereas serum exhibits only a slight enzymatic hydrolysis of acetyl-β-methylcholine, the cells produce an enzymatic scission at a rate which is of the same order as that of acetylcholine.

(2) Mendel and Rudney[3] observed that purified preparations derived from serum and certain tissues exhibited enzymatic hydrolysis of acetylcholine, tributyrin and methyl butyrate, while those obtained from brain tissue and the red blood cells of some mammals possessed demonstrable activity only on the acetylcholine. These workers concluded that a non-specific enzyme, for which they proposed the name "pseudocholinesterase," was present in the former case and a specific cholinesterase in the latter.

(3) In a later communication Mendel, Mundell and Rudney[4] reported that acetyl-β-methylcholine was

[1] G. A. Alles and R. C. Hawes, *Jour. Biol. Chem.*, 133: 375, 1940.

[2] R. C. Hawes and G. A. Alles, *Jour. Lab. Clin. Med.*, 26: 845, 1941.

[3] B. Mendel and H. Rudney, *Biochem. Jour.*, 37: 59, 1943.

[4] B. Mendel and D. B. Mundell and H. Rudney, *Biochem. Jour.*, 37: 473, 1943.

hydrolyzed by "true," but not by "pseudo," cholinesterase, and benzoylcholine was split by the "pseudo," but not by the "true," enzyme. These specificities were proposed as a basis for the separate estimation of the two enzymes. No reference was made in this publication to the previous work of Alles and Hawes[1] on the differences in the enzymatic effect of blood cells and serum on acetyl-β-methylcholine.

(4) The controversy in SCIENCE began with the restatement by Mendel and Rudney,[5] on the basis of their findings alone and without reference to the work of Alles and Hawes, that separate "true" and "pseudo" cholinesterases exist.

(5) A claim of priority for Alles and Hawes as the discoverers of two distinct enzymes capable of effecting the hydrolysis of acetylcholine was submitted by de Laubenfels,[6] who also referred to the term "pseudo-cholinesterase" as an unfortunate designation, since most of the work already in the literature on the enzymatic scission of choline esters dealt with the activity of the "pseudo" enzyme but had always been called simply cholinesterase.

(6) Mendel and Rudney[7] countered with the statement that Alles and Hawes were not aware of the existence of a specific and a non-specific enzyme, and emphasized that the serum, that Alles and Hawes found possesses enzyme properties different from those of the blood cells, actually contains both types of cholinesterase. Mendel and Rudney then defended their term "pseudo-cholinesterase" on the ground that the "pseudo" emphasizes non-specificity; they referred to their previous suggestion that the term be provisional until the physiological function of the enzyme is established.

(7) Alles and Hawes[8] supported de Laubenfels in regard to the use of "pseudo-cholinesterase," and reaffirmed their priority for the discovery of the two enzymes.

(8) A final review of the situation was given by Mendel and Rudney,[9] in which they pointed out that the view of Alles and Hawes, that the two types of cholinesterase exist separately in human serum and blood cells, must be modified in the light of later findings showing that the serum contains a small proportion of the "cell enzyme," and furthermore biological localization of these enzymes varies from one species to the next. Mendel and Rudney then claimed that it was only their own work on specificity with purified preparations that furnished the proof of the existence of two enzymes. Finally they again repeated the reason for their innovation in nomenclature.

[5] B. Mendel and H. Rudney, SCIENCE, 98: 201, 1943.
[6] M. W. de Laubenfels, SCIENCE, 98: 450, 1943.
[7] B. Mendel and H. Rudney, SCIENCE, 99: 37, 1944.
[8] G. A. Alles and R. C. Hawes, SCIENCE, 100: 75, 1944.
[9] B. Mendel and H. Rudney, SCIENCE, 100: 499, 1944.

From the foregoing recapitulation it is clear that, if one accepts the evidence reported thus far as proof for the existence of two separate cholinesterases, Alles and Hawes deserve the priority for the initial discovery which Mendel and Rudney confirmed and considerably extended. The possibility should be kept in mind that the specificities observed for cholinesterases may still be found to result not from the enzyme itself, but rather from other factors or concomitant substances associated with the enzyme. But in regard to the specificity as it stands to-day, it was Alles and Hawes who first demonstrated the different actions of two enzyme preparations on acetyl-β-methylcholine. The fact that one of the preparations, human serum, was shown subsequently to contain a small proportion of the other enzyme factor in no way detracts from their use of this substrate in contributing toward the enzyme differentiation. It was only natural for Alles and Hawes in 1939, when the first information was coming to light, to refer to the two factors as blood cell enzyme and serum enzyme as a matter of convenience, but they did not advocate that the names "'cell-cholinesterase" and "serum-cholinesterase" be adopted as official designations, and they used differences in properties, rather than locale, as their criteria.

If any one encountering the term "pseudo-cholinesterase" were to understand that "pseudo-" was meant to indicate non-specific, there would be no difficulty. However by definition "pseudo-" means false, and many might logically puzzle themselves with the question, "Just what is a pseudo-enzyme?" In truth, the writer has yet to speak to a single enzyme chemist who favors the term "pseudo-cholinesterase." However, though the undesirability of the term is apparent and it should be dropped from the literature, it is difficult to find one entirely adequate. With full knowledge of their shortcomings, the terms, specific and non-specific cholinesterase, might suffice until more knowledge is available; at least their connotation is less undesirable. In fact, these terms have been actually employed at times by Mendel and Rudney.

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THE GENETIC DESIGNATION OF "STRAIN" IN BACTERIOLOGY

THE recent article in SCIENCE on "The Concept of a 'Strain' in Bacteriology," by George H. Chapman,[1] leaves much to be desired. One may well question the statement "Because of the strong dissociative tendency among many bacteria which tends to produce distinctly different daughter races from apparently

[1] SCIENCE, 101: 429–430, 1945.

homogeneous parent cultures, transplants of such colonies are frequently considered as separate 'strains,'" because its major premise is that the parent cultures are apparently homogeneous. Most bacteriologists use the term "strain" for any independent culture, although various of these cultures or strains might prove to be apparently identical and belong in one "type" or "variety."

When dissociation occurs it may be of two kinds, "phenotypic" or temporary and "genotypic" or permanent. Still another occurrence is that of loss of virulence by pathogenic species in which the cultural and physiological characteristics may remain essentially unchanged. This poses the question: Is there a reliable method for accurately determining when a bacterial culture becomes genetically unrelated to its parent or sister cultures to enable one to designate the progeny as cultures or strains? The reservation of the designation of "strain" for the "offspring of a single 'pure' culture or better still, of a single cell" is a restricted form of definition because it leaves out of account the fact that all cultures are the progeny of single colonies or cells, pure or mixed, even though they are not designated and known as such. Several years ago the writer[2] discussed the pure culture concept in relation to microorganisms, pointing out the range in its interpretation by different investigators. The suggestion that strains "should only be considered as such when it is known that they are genetically unrelated" is an order quite out of reach and keeping with present methods and knowledge.

It is probable that most bacteriologists would be confused by the genetic appellation being considered as basic to the use of the term "strain" in bacteriology. After all is said and done, the terminology all scientists should be striving for is one that describes but does not confuse the scientist or layman of this or some related science. Just as the social sciences are jargon-ridden to their serious detriment, so also are some of the biological sciences cultivating confusion rather than understanding as fads come and go or grow.

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EXPERIMENTAL TUMORS IN AN INSECT

AMONG the conditions which bring about the development of tumors such factors as hormones, nutrition, carcinogenic substances and others are currently studied by many workers in vertebrates, particularly in mammals. This preliminary note concerns an experimental animal not commonly used in tumor research, namely an insect (*Leucophaea maderae*, Orthoptera), and a factor, not usually considered as playing a role in tumorous growth, *i.e.*, innervation.

[2] E. M. Hildebrand, *Bot. Rev.*, 4: 627–664, 1938.

Innervation as a factor in the origin of tumors was studied by cutting the recurrent nerve at various levels. As in other insects this nerve, together with several sympathetic ganglia, represents the stomatogastric nervous system. The branches of the recurrent, which innervate the anterior portion of the alimentary canal as well as the salivary glands and their reservoir, were demonstrated in methylene blue preparations. When the recurrent nerve was cut tumors developed within ten days to several months after the operation in organs innervated by the recurrent nerve, *i.e.*, in the salivary glands, the salivary reservoir and the anterior gut. To date about 250 specimens with experimental tumors were obtained in this way. The tumors which may attain considerable sizes were verified by dissection of the animals, and many of them were cut for histological study.

Histologically the tumors consist of layers of cells which show various degrees of abnormality. In advanced stages the cells near the lumen of the organ, for instance, of the mid-gut, frequently break down into a brownish debris. The anterior portion of the mid-gut is a common site of these tumors. They are also frequently found in the wall of the salivary reservoir where they are particularly conspicuous because normally the wall is a very thin and transparent membrane. In the fore-gut and in the salivary glands well-developed tumors are relatively rare.

Several hundred animals were operated upon in various other ways (allatectomy, castration, etc.), care being taken not to disturb the recurrent nerve. These control operations did not cause the development of tumors. A more detailed report, to be published elsewhere, is in preparation.

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THE SHORTAGE OF SCIENTIFIC PERSONNEL

I HAVE read with great interest the series of discussions and articles in SCIENCE relating to the shortage of trained scientists in this country. As a professional scientist (zoology, general physiology) the matter is of personal concern to me.

However, I have noticed that all the writers, who bewail the future results of the shortage, fail to consider one factor: the large number of highly trained scientists (Ph.D.'s) who are temporarily in the Armed Forces. The vast majority of these are anxious to return to a normal civilian position as soon as possible. They should be carefully considered whenever one discusses the dearth of scientists.

As a first-hand example, may I take my present occupation in aviation physiology with the Army Air Forces? There are well over a hundred aviation

physiologists in the service. All of us have the degree of doctor of philosophy in one of the biological (broad sense) sciences. We teach and do research in connection with problems of respiration, anoxia, air sickness, body temperature, and the like. With only one or two exceptions we are all anxious to return to academic life. We are an available pool of young scientists who will need positions when the war is over. In the Army Sanitary Corps, in the Quartermaster Corps and in the Navy you will find similar men.

However, we feel rather ignored, since practically none of us has been offered a civilian position to become effective upon discharge from the service. If the shortage of scientists is so critical and if the various university and commercial representatives are sincere, why have not the scientists, who are now temporarily in uniform, been approached in regard to post-war appointments?

Personally, the outlook is not too bright. Most university men with whom I have spoken recently maintain that they are making no postwar plans to take on additional faculty members. Where, then, does the shortage exist?

We have noticed that the National Research Council is planning to grant fellowships to aid young scientists in studying for the doctorate. We have not heard of any plan whereby trained scientists (now in the service) can get a six-month period of rehabilitation and "refreshing" between the time of discharge and the time they enter into new civilian duties.

CHARLES G. WILBER

SCIENTIFIC BOOKS

CHARLES DAVIES SHERBORN

Squire: Memoirs of Charles Davies Sherborn. By J. R. NORMAN. 202 pages. 2 figs., 8 plates. London: George G. Harrap and Co. 1944. 15 shillings.

"SQUIRE" was a unique character among British scientists, and this biography by one of the most intimate friends of his later years is in many respects a unique book. By means of personal recollections, excerpts from Sherborn's letters and autobiographical notes and various anecdotes and reminiscences supplied by friends and colleagues, it re-creates the spirit of the man and reveals an aspect of the scientific life that is seldom seen in any country. It moreover gives an extraordinary insight into the working relationships of the group of famous scientists who brought honor to the British Museum and other official organizations and learned societies of England, as well as to themselves, in the last quarter of the nineteenth century and the first quarter of the twentieth century. Many an American zoologist, geologist and student of the history of science will gain much pleasure as well as profit by reading it.

Dr. Sherborn was a "born collector" and even before he left school in 1875, at the age of fourteen, he "had amassed quite useful series of shells, fossils, minerals, stamps, coins, books, autograph letters, historical and other documents, and even a few prints." Despite his lack of any advanced formal schooling, his entire life was spent in close association with research scientists and he not only helped many of them achieve success, but he made many contributions to knowledge on his own account, notably in stratigraphic geology, paleontology and zoology. His *magnum opus* was of course the *Index Animalium,* with its 440,000 references, the last part of which was issued in 1933. This monumental work involved the indexing of nearly 28,000 publications and was completed only after forty-three years of unremitting toil in the face of difficulties that required almost superhuman persistence to surmount. Would that all the thousands of scientists the world around who blithely consult it from time to time could be required to read Mr. Norman's account of the way this self-assigned task was accomplished! Surely they would all applaud the action of Oxford University in conferring upon "Squire" Sherborn the honorary degree of doctor of science, the only academic reward and almost the only official recognition he ever received throughout his long life of unselfish, quiet service in the cause of science.

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THE BIRDS OF CALIFORNIA

The Distribution of the Birds of California. By JOSEPH GRINNELL and ALDEN H. MILLER. Cooper Ornithological Club, Pacific Coast Avifauna No. 27. 608 pp., 1 color plate, 57 maps. Berkeley, Calif., 1944.

THE physiography of California and its effect upon meteorological phenomena have produced a notably large number of ecological niches. These are characterized not only by climates that can be quantitatively defined, but also by special associations of plants and animals. In extreme examples, such as that of the yellow-billed magpie, the correlation is one of thoroughgoing endemism. This bird (*Pica nuttallii*) occurs nowhere outside its limited range within the State of California.

Aside from climate of the proper kind, a further probably essential factor in habitable environment is presence of accessible water in dry seasons, needed not only to drink but in certain phases of nest-building; another is

relatively gentle winds rather than regular, strong winds, which factor seems in itself to bar this magpie from certain otherwise suitable areas. The total of requirements for the yellow-billed magpie is thus distinctly different from that of the American Black-billed Magpie . . . ; neither species would likely thrive for long within the range of the other [p. 294].

For sixty years the taxonomic and distributional study of California birds has been the interest of an extremely active group of ornithologists. The late Dr. Joseph Grinnell, senior author of the present monograph, often said that continuation of the undertaking offered problems enough to keep a growing company of workers busy for the next hundred years. His statement may be true, provided constant extension of the aims is taken into account, though it is difficult to see how any refinement of technique could broaden the scope or improve the usefulness of the present volume without rapidly encountering limitations imposed by the law of decreasing returns.

The work covers 427 species (644 species and subspecies) of California birds. Of these, 273 species (423 species and subspecies) breed within the State. 84 species are represented by more than 1 race: 38 by 2 races, 21 by 3, 11 by 4, 3 by 5, 3 by 6, 3 by 7, and single species have, respectively, 8, 10, 13, 15 and 18 races. California song sparrows comprise no fewer than 14 races, the breeding ranges of several of which are restricted to extremely small ecological niches. A colored frontispiece portrays the distinctive plumage characters of eight of these forms, and a distributional map on page 548 shows the ranges within the State of all 14.

After an introduction of eight pages, the work opens with a systematic list of the species and subspecies of California birds. This includes both technical and vernacular names, in both of which the authors make certain departures from the A. O. U. Check-List of North American Birds, a step taken deliberately and ably defended in the introduction. Then follows the general account of the native birds of the State, which occupies the bulk of the volume. The treatment includes a list of synonyms; a paragraph on the status of the form in California; a longer paragraph on the geographic range, which lists the published sources and gives a succinct and illuminating insight into the nature of earlier findings. The final heading under each form relates to the habitat of the bird within its seasonal or permanent geographic range. A total of 57 clear distributional maps adds greatly to the usefulness of the admirable text.

Pages 557 to 576 are devoted to introduced species and to those of uncertain or legendary status. By such means the authors have removed from the body of their book material of a kind that has long cluttered up the text of countless other works on ornithology, while at the same time they have not deprived their readers of information that has a special interest in its own right. The work closes with an index covering all scientific and popular names of every species and subspecies.

The book as a whole fulfils expectations built up by the senior author, who is no longer living, and the junior author, who still carries on in the same tradition. There is not a word of padding in its 608 pages. Its text is stark but sufficient, and it offers a direct guide to the best sources of more detailed information. Space precludes further consideration of a particular sample of the text, but the reviewer can not forbear a reference to the common cliff swallow of California which, according to seasonal press releases, arrives each year at the mission of San Juan Capistrano on March 19 and departs with equal regularity on October 23, taking due account, if we are to believe the newspapers, even of the quadrennial shift produced by leap year. Grinnell and Miller have no space in their compact text for a reference to the pious tale, but in discussing the status of this swallow in California they note that the "dates of arrival and departure are greatly variable with year and locality."

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